IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant(s):	Martis et al.
Appl. No.:	09/955,248
Conf. No.:	8992
Filed:	September 17, 2001
Title:	BIOCHEMICALLY BALANCED PERITONEAL DIALYSIS SOLUTIONS
Art Unit:	1621
Examiner:	R. Keys
Docket No.:	DI-4641 CONT

#17
9/4/03

Commissioner for Patents

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APPELLANTS' APPEAL BRIEF

Dear Sir:

This Appeal Brief is submitted in support of the Notice of Appeal submitted by Appellants on June 6, 2003 in the above-identified patent application. This Appeal is taken from the Final Rejection dated January 14, 2003.

I. REAL PARTY IN INTEREST

The real party in interest for the above-identified patent application on Appeal is Baxter International Inc. by virtue of an Assignment recorded at the United States Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES

Appellants do not believe there are any known appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision with respect to the above-identified Appeal.

III. STATUS OF THE CLAIMS

Claims 1-16 are pending in this application. A copy of appealed Claims 1-16 is attached in the appendix. In the Final Office dated January 14, 2003, Claims 1, 2 and 4-8 stand rejected as

allegedly anticipated by *Peritoneal Dialysis International*, Vol. 13, Suppl. 2, October 1992, pp. S116 – S118 ("*Schambye*") in view of U.S. Patent No. 5,296,242 ("*Zander*"); Claims 1, 2 and 4-8 stand rejected as allegedly anticipated by U.S. Patent No. 4,663,166 ("*Veech I*") in view of *Zander*; Claims 1-10 stand rejected as allegedly obvious in view of *Schambye* and *Zander*; Claims 1-16 stand rejected as allegedly obvious in view of *Veech I* and *Zander*; and Claims 1-16 stand rejected as allegedly obvious in view of U.S. Patent No. 6,020,007 ("*Veech II*") and *Zander*. A copy of the Final Office Action is appended hereto as Exhibit A of the Supplemental Appendix and a copy of each of the cited references is appended hereto as Exhibits B-E of the Supplemental Appendix.

IV. STATUS OF THE AMENDMENTS

No Amendments After Final were filed.

V. SUMMARY OF THE INVENTION

The present invention relates generally to peritoneal dialysis. More specifically, the present invention relates to peritoneal dialysis solutions. (Specification, p. 1, lines 6-8.)

It is known to use dialysis to support a patient whose renal function has decreased to the point where the kidneys no longer sufficiently function. Two principal dialysis methods are typically utilized, namely hemodialysis and peritoneal dialysis. (Specification, p. 1, lines 9-13.)

To overcome the disadvantages associated with hemodialysis, peritoneal dialysis was developed. Peritoneal dialysis utilizes the patient's own peritoneum as a semi-permeable membrane. The peritoneum is the membranous lining of the abdominal cavity that due to a large number of blood vessels and capillaries is capable of acting as a natural semi-permeable membrane. (Specification, p. 1, lines 20-26.)

In peritoneal dialysis, a dialysis solution is introduced into the peritoneal cavity utilizing a catheter. After a sufficient period of time, an exchange of solutes between the dialysate and the blood is achieved. Fluid removal is achieved by providing a suitable osmotic gradient from the blood to the dialysate to permit water outflow from the blood. This allows the proper acid-base of

electrolytes and fluid balance to be returned to the blood, and the dialysis solution is simply drained from the body cavity through the catheter. (Specification, p. 1, line 27 to p. 2, line 3.)

A number of dialysis solutions have been utilized and suggested. For example, lactate has been utilized in peritoneal dialysis solutions for the purpose of maintaining acid-base balance in peritoneal dialysis patients. Typical commercially available peritoneal dialysis solutions contain 35 to 40 mEq/L of lactate. (Specification, p. 2, lines 4-22.)

These solutions are adequate in maintaining acid-base balance in a number of dialysis patients. However, patients who are deficient in lactate metabolism and/or who also experience or suffer from hepatic failure or shock, can develop lactic acidosis. This syndrome includes as characteristic symptoms hyperventilation, abdominal pain, and disturbances in consciousness while the patient receives lactate-containing peritoneal dialysis fluids. (Specification, p. 2, lines 23-32.)

An additional issue with respect to lactate peritoneal dialysis solutions is that a number of *in vitro* studies performed with peritoneal cells indicate that altered cell function can occur when peritoneal cells are exposed to large concentrations of lactate. These changes in cell function can compromise host defense leading to increased rates of infection and damage to the peritoneal membrane. (Specification, p. 2, line 31 to p. 3, line 6.)

In order to address this issue, peritoneal dialysis solutions in which lactate is completely replaced by bicarbonate have been proposed. However, in order to balance total body hydrogen ion content against metabolically generated hydrogen, and to maintain normal plasma carbonic acid and bicarbonate concentrations, it is necessary to use bicarbonate concentrations that are considerably in excess of normal. In this regard, bicarbonate concentration upwards of 38 mM/L are believed to be necessary. (Specification, p. 3, lines 6-15.)

Because it is necessary to maintain the solution at a physiological pH, the requirement of such a high bicarbonate solution requires a partial pressure of carbon dioxide (pCO_2) that is at least twice the physiologic pCO_2 (e.g., greater than 80 mmHg). Although such a solution may meet the metabolic needs of the patient, such a solution does not provide a physiological environment for the peritoneal cells in contact with the solution. Due to the differences in transport rates between bicarbonate and carbon dioxide, with such a solution, the intracellular hydrogen ion concentration of the cell's lining the peritoneal cavity, as well as those present in the peritoneal cavity, would be

severely low placing them at a metabolic disadvantage. This metabolic disadvantage will increase more than would be expected if they share the extracellular environment of normal pH, but a supernormal bicarbonate and pCO_2. (Specification, p. 3, lines 16-32.)

The present invention provides improved peritoneal dialysis solutions. The solutions are biochemically balanced to correct metabolic acidosis that is associated with chronic renal failure. Pursuant to the present invention, the solutions are biochemically balanced in a more physiological manner than prior peritoneal solutions. (Specification, p. 7, lines 6-12.)

To this end, the present invention provides peritoneal dialysis solutions that contain bicarbonate at a more physiological level, e.g., at a level substantially equivalent to that found in normal blood. The peritoneal dialysis solution of the present invention, in an embodiment, includes bicarbonate present at a level of approximately 20 mM/L to about 30 mM/L. In a most preferred embodiment, bicarbonate is present at a level of 25 mM/L. (Specification, p. 7, lines 13-23.)

Additionally, the solution contains carbon dioxide at a partial pressure that is less than 60 mmHg. In a preferred embodiment the pCO_2 of the solution is similar to the partial pressure of carbon dioxide found in blood capillaries. Further, preferably, the dialysis solutions have a pH of 7.4. Therefore, the solution, although balanced biochemically, is a physiologically acceptable solution. (Specification, p. 7, lines 24-31.)

Additionally, the solutions include a weak acid with a pKa of less than 5. These weak acids are chosen so as to be normal biochemical intermediates of glucose metabolism. Preferably, the weak acids can include: lactate; pyruvatet citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate. These acids can be present either alone or in combination in the solution. Preferably, the weak acids are present at a level of approximately 10 to about 20 mEq/L. Preferably, the weak acids are present mainly as sodium salts. The weak acid is present in an amount that would offset the daily metabolic hydrogen production of approximately 1 mEq/kg/day. (Specification, p. 7, line 32 to p. 8, line 12.)

Pursuant to the present invention, any osmotic agent can be used in the solution. For example, dextrose, maltodextrin, glycerol, polyglucose, polypeptides and amino acids can be used as the osmotic agent. (Specification, p. 8, lines 12-16.)

In an embodiment, the peritoneal dialysis solution, if it contains dextrose as an osmotic agent, has a general composition such as that set forth below:

Dextrose (hydrous) (g/dl)	1.5-4.25
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0
Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-20.0
pH	7.0-7.4

(Specification, p. 8, lines 17-27.)

In an embodiment, solutions containing an osmotic agent other than dextrose composition have the general composition:

Osmotic agent (mM/L)	1-200
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0
Bicarbonate (mEq/L)	20.0-30.0
Weak Acid (mEq/L)	10-20.00
pH	7.0-7.4

(Specification, p. 8, line 28 to p. 9, line 5.)

The peritoneal dialysis solutions of the present invention balance bicarbonate at normal concentrations and have a pCO_2 at normal partial pressure. The weak acid under usual circumstances will have an infinite gradient from dialysate to blood. Thus, the weak acid can be expected to perform in a relatively predictable manner in correcting the metabolic acidosis of chronic uremia. (Specification, p. 9, lines 6-13.)

Due to the composition of the present invention, should the patient's bicarbonate level drop below prescribed normal blood figure of 25 mM/L, then there will be an additional contribution by diffusion of bicarbonate to offset the unbalanced metabolic hydrogen load and *vice versa* for a supernormal concentration. Phrased in a different manner, the solution has a built-in servo mechanism around the figure of 25 mM/L for bicarbonate. A pure bicarbonate solution at higher than normal concentrations does not offer this benefit. (Specification, p. 9, lines 14-23.) By way

of example, and not limitation, Appellants have provided a number of specific peritoneal dialysis solutions pursuant to an embodiment of the present invention. (Specification, p. 9, lines 24-26.)

VI. ISSUES

The issues on Appeal are as follows:

1. Would the peritoneal dialysis solutions as defined in Claims 1, 2 and 4-8 have been novel over *Schambye* in view of *Zander*?

2. Would the peritoneal dialysis solutions as defined in Claims 1, 2 and 4-8 have been novel over *Veech I* in view of *Zander*?

3. Would the peritoneal dialysis solutions as defined in Claims 1-10 have been obvious in view of *Schambye* and *Zander*?

4. Would the peritoneal dialysis solutions and methods for reducing acidosis as defined in Claims 1-16 have been obvious in view of *Veech I* and *Zander*?

5. Would the peritoneal dialysis solutions and methods for reducing acidosis as defined in Claims 1-16 have been obvious in view of *Veech II* and *Zander*?

VII. GROUPING OF THE CLAIMS

Appellants argue for the separate patentability of each of the independent claims separate and apart from each other set forth in detail below pursuant to the requirements of 37 C.F.R. § 1.192(7), unless otherwise specified.

VIII. ARGUMENT

A. The Claimed Invention -- Independent Claims

On appeal, Claims 1, 6, 10 and 11 are the sole independent claims. Independent Claims 1, 6, 10 and 11 are provided below as follows:

Independent Claim 1 recites a peritoneal dialysis solution. The peritoneal dialysis solution includes bicarbonate at a level of less than or equal to 30 mM/L, a carbon dioxide partial pressure

that is less than 60 mmHg and at least one weak acid at a level of between approximately 15 mEq/L and approximately 20 mEq/L wherein the weak acid includes lactate, pyruvate, citrate, isocitrate, cis-aconitase, α-ketoglutarate, succinate, fumarate, malate, and oxaloacetate.

Independent Claim 6 recites a peritoneal dialysis solution. The peritoneal dialysis solution includes Dextrose, Sodium, Chloride, Calcium, Magnesium, Bicarbonate and a weak acid in specified amounts wherein the weak acid includes lactate, pyruvate, citrate, isocitrate, cis-aconitase, α-ketoglutarate, succinate, fumarate, malate, oxaloacetate or mixtures thereof. The peritoneal dialysis solution further includes a carbon dioxide partial pressure that is less than 60 mmHg.

Independent Claim 10 recites a peritoneal dialysis solution that includes Dextrose, Sodium, Chloride, Calcium, Magnesium, Bicarbonate and a weak acid in specified amounts, wherein the weak acid includes lactate, pyruvate, citrate, isocitrate, cis-aconitase, α-ketoglutarate, succinate, fumarate, malate, oxaloacetate, or mixtures thereof. The peritoneal dialysis solution further includes a carbon dioxide partial pressure that is substantially similar to the carbon dioxide partial pressure of a normal subject's blood wherein the solution has a pH of approximately 7.0 to about 7.4.

Independent Claim 11 recites a method for correcting metabolic acidosis in a dialysis patient suffering or likely to suffer from same. The method includes administering to a patient a peritoneal dialysis solution that has a bicarbonate level and carbon dioxide partial pressure that are substantially similar to that found in the patient's blood wherein the solution includes Dextrose, Sodium, Chloride, Calcium, Magnesium, Bicarbonate and a weak acid in specified amounts.

B. The Rejection

Claims 1-16 have been rejected under 35 U.S.C. § 102 and/or § 103. The Patent Office essentially asserts that the cited art discloses or suggests each of the features of the claimed invention. In this regard, the Patent Office has relied on *Zander* in combination with *Veech I*, *Veech II* or *Schambye* in support of the anticipation and obviousness rejections.

C. Claims 1-16 are Novel and Nonobvious

Appellants respectfully submit that the rejections under 35 U.S.C. § 102 and § 103 should be reversed based on the fact that the Patent Office has failed to establish a *prima facie* case of anticipation and obviousness. Appellants submit that the cited references, even if combinable, fail to disclose or suggest at least a number of features of the claimed invention. Further, Appellants believe that the Patent Office has relied on hindsight reasoning for combining and/or modifying the cited art in support of the rejections.

1. The Applicable Law

"Under 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in the prior art ..." *Akzo NV v. U.S. International Trade Commission*, 1 U.S.P.Q. 2d 1241, 1245 (Fed. Cir. 1986). The Court of Appeals for the Federal Circuit has held that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a *single* prior art reference." *Verdegaal Bros. v. Union Oil of California,* 814 F.2d 628, 631 (Fed. Cir. 1988) (*emphasis added*).

The Federal Circuit has held that the legal determination of an obviousness rejection under 35 U.S.C. § 103 is:

> whether the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made...The foundational facts for the prima facie case of obviousness are: (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; and (3) the level of ordinary skill in the art...Moreover, objective indicia such as commercial success and long felt need are relevant to the determination of obviousness...Thus, each obviousness determination rests on its own facts.

In re Mayne, 41 U.S.P.Q.2d 1451, 1453 (Fed. Cir. 1997).

In making this determination, the Patent Office has the initial burden of proving a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). This burden may only be overcome "by showing some objective teaching in the prior art or

that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings." *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). "If the examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Further, the Federal Circuit has held that it is "impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention" *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988).

Moreover, the Federal Circuit has held that "obvious to try" is not the proper standard under 35 U.S.C. §103. *Ex parte Goldgaber*, 41 U.S.P.Q.2d 1172, 1177 (Fed. Cir. 1996). "An-obvious-to-try situation exists when a general disclosure may pique the scientist curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claim result would be obtained if certain directions were pursued." *In re Eli Lilly and Co.*, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).

2. The Rejections under 35 U.S.C. §102 and §103 Should Be Reversed Because the Patent Office Has Failed to Establish a *Prima Facie* Case of Anticipation and Obviousness

Appellants respectfully submit that the Patent Office has failed to overcome its *prima facie* burden with respect to the rejections of the claimed invention under 35 U.S.C. §102 and §103. At the outset, the Patent Office has improperly relied on the combined teachings of *Zander* with *Schambye* or *Veech I* in support of the anticipation rejections. Even if *Zander* is properly combinable with respect to the cited art, the peritoneal dialysis solutions and methods of reducing acidosis of the claimed invention are not anticipated nor rendered obvious in view of same. Indeed, Appellants believe that the Patent Office has relied on hindsight reasoning in support of same.

a. The Peritoneal Dialysis Solution Features of the Claimed Invention

Of the pending claims, Claims 1, 6, 10 and 11 are the sole independent claims. As set forth in independent Claim 1, the peritoneal dialysis solution of the present invention includes a bicarbonate concentration of less than or equal to 30 mM/L, a carbon dioxide partial pressure that is less than 60 mmHg and at least one weak acid at a concentration between 15 mEq/L and approximately 20 mEq/L which is selected from the group consisting of lactate, pyruvate, citrate, isocitrate, cis-aconitase, α-ketoglutarate, succinate, fumarate, malate and oxaloacetate. Acetate is not one of the weak acids which is used in the solution of the present invention.

Claims 6 and 10 require the peritoneal dialysis solution to include dextrose, sodium, chloride, calcium, magnesium, bicarbonate in a range from 20.0 to 30.0 mEq/L, and at least one weak acid in a concentration from 10 to 20 mEq/L that is chosen from the group consisting of lactate, pyruvate, citrate, isocitrate, cis-aconitaase, α-ketoglutarate, succinate, fumarate, malate and oxaloacetate. The solution of Claim 6 also has a carbon dioxide partial pressure that is less than 60 mmHg. The solution of Claim 10 has a carbon dioxide partial pressure that is similar to the partial pressure of a normal subject's blood and further has a pH of 7.0 to 7.4.

The method of Claim 11 includes the step of administering to the patient a peritoneal dialysis solution that has a bicarbonate level and a carbon dioxide partial pressure that is substantially similar to that found in the patient's blood and which further includes dextrose, sodium, chloride, calcium, magnesium, bicarbonate in a concentration ranging from 20 to 30 mEq/L, and a weak acid in a concentration ranging from 10 to 20 mEq/L.

The present invention provides peritoneal dialysis solutions that are biochemically balanced to correct metabolic acidosis associated with chronic renal failure in a more physiological manner. In this regard, the peritoneal dialysis solutions of the present invention have a physiological pH and contain bicarbonate at a concentration that is found in blood involved in diffusive transport of solutes with dialysis fluid. This will block the loss of bicarbonate during peritoneal dialysis, which is the case with known solutions. Additionally, the solutions contain carbon dioxide at a partial pressure that is similar to a partial pressure of carbon dioxide found in the blood capillaries. The peritoneal

dialysis solutions also contain a weak acid at a specified amount needed to neutralize acid generated from endogenous metabolism. These weak acids are also the normal biochemical intermediates of glucose metabolism resulting in neutral end products. See, Specification, page 4, lines 7-24.

b. The Cited References Fail to Disclose or Suggest the Peritoneal Dialysis Solution Features of the Claimed Invention

Appellants believe that the cited art, even if properly combinable, fails to disclose or suggest the claimed invention. Therefore, Appellants believe that the anticipation and obviousness rejections are clearly improper.

At the outset, the Patent Office has improperly relied on *Zander* in support of the anticipation rejections with respect to Claims 1, 2 and 4-8. Of these claims, Claims 1 and 6 are the sole independent claims that each relate to peritoneal dialysis solutions as previously discussed. The peritoneal dialysis solution of Claim 1 includes, in part, a bicarbonate concentration of less than or equal to 30 mM/L, a carbon dioxide partial pressure that is less than 60 mmHg and at least one weak acid not including acetate at a concentration between 15 mEq/L and approximately 20 mEq/L. Claim 6 recites a peritoneal dialysis solution that includes, in part, a bicarbonate concentration that ranges from 20.0 mEq/L to 30.0 mEq/L, a carbon dioxide partial pressure that is less than 60 mmHg and a weak acid not including acetate at a concentration from 10 mEq/L to 20 mEq/L.

Of course, "[a]nticipation requires the disclosure in a *single* prior art reference of each element of the claim under consideration." *W.L. Gore and Associates v. Garlock Inc.*, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983) *emphasis added.* Indeed, the Court of Appeals for the Federal Circuit has held that "[w]hen more than one reference is required to establish unpatentability of the claimed invention, anticipation under § 102 cannot be found, and validity is determined in terms of § 103. *Continental Can Co. U.S.A. v. Monsanto Co.*, 20 U.S.P.Q.2d 1746, 1748 (Fed. Cir. 1991). This clearly applies to the present case contrary to the Patent Office's position.

In this regard, the Patent Office explicitly relies on a secondary reference, namely *Zander*, in support of each of the anticipation rejections. Moreover, the Patent Office rejects the same claims

in view of the same references in separate obviousness rejections. This clearly suggests that the Patent Office intended to reject Claims 1, 2 and 4-8 under 35 U.S.C. § 103 and not § 102.

Even assuming that the Patent Office can rely on *Zander*, which it cannot, Appellants respectfully submit that the cited references fail to disclose the claimed invention. For example, nowhere does the cited art disclose a peritoneal dialysis solution that combines a specified bicarbonate and weak acid concentration in addition to a specific carbon dioxide partial pressure effective in maintaining an acid-base balance in dialysis patients as required by the claimed invention. Indeed, *Schambye* and *Veech I* each at least fail to disclose the carbon dioxide partial pressure features of the claimed invention as even admitted by the Patent Office.

Further, the claimed invention is not inherent in view of the cited art. Of course, "inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 212 U.S.P.Q. 323, 326 (CCPA 1981) (quoting *Hansgirg v. Kemmer*, 40 U.S.P.Q. 665, 667 (CCPA 1939). Again, *Schambye* or *Veech I* fail to disclose the claimed carbon dioxide partial pressure features, let alone in combination with the claimed bicarbonate and weak acid features, as previously discussed.

Moreover, *Zander* cannot be relied on to demonstrate that the claimed features are inherent in view of *Schambye* or *Veech I.* Indeed, *Zander* effectively teaches away from the peritoneal dialysis solutions as required by the claimed invention. For example, while *Zander* may disclose a carbon dioxide partial pressure of 40 mmHg, this solution lacks a weak acid component, thus rendering it deficient in terms of neutralizing hydrogen ions generated endogenously by the dialysis patient as a result of protein metabolism. See, *Zander*, col. 2, lines 35-43.

Zander also discloses a solution that combines bicarbonate and acetate at a concentration of 27.2 mmole/l. See, *Zander*, col. 6, lines 47-53. Indeed, the peritoneal dialysis solutions do not include acetate as a weak acid as defined in Claims 1 and 6. Further, this weak acid concentration (e.g., acetate and/or other weak acid concentration) is too high to be effective for maintaining the acid-base balance. Appellants' position with respect to the *Zander* reference is supported by the Declaration of Dr. Leo Martis that was previously submitted in support of Appellants' Amendment filed on April 30, 2002. See, *Martis* Declaration, ¶¶ 4-6, a copy of which is attached hereto as Exhibit F. In view of same, Appellants believe that one skilled in the art would consider the

peritoneal dialysis solutions of the claimed invention distinguishable from the cited art. Therefore, Appellants believe that the anticipation rejections are clearly erroneous in law and in fact.

With respect to the obviousness rejections, Claims 1-10 stand rejected in view of *Schambye* and *Zander*; Claims 1-16 stand rejected in view of *Veech I* and *Zander*; and Claims 1-16 stand rejected in view of *Veech II* and *Zander*. Of the pending claims at issue, Claims 1, 6, 10 and 11 are the sole independent claims. Claims 1 and 6 recite peritoneal dialysis solutions as previously discussed. Claim 10 recites a peritoneal dialysis solution that includes, in part, a weak acid (not including acetate) at a concentration from 10 mEq/L to 20 mEq/L, a bicarbonate concentration from 20 mEq/L to 30 mEq/L, a carbon dioxide partial pressure that is similar to the partial pressure of a normal subject's blood, and a pH of 7.0 to 7.4.

Claim 11 recites a method for correcting metabolic acidosis that includes, in part, the step of administering to a patient a peritoneal dialysis solution with a bicarbonate level and a carbon dioxide partial pressure that is substantially similar to that found in the patient's blood and further a bicarbonate concentration and a weak acid concentration that ranges from 20 to 30 mEq/L and from 10 mEq/L to 20 mEq/L, respectively. Again, the claimed peritoneal dialysis solutions are biochemically balanced to correct metabolic acidosis associated with chronic renal failure in a more physiological manner.

In contrast, the primary references, namely, *Schambye*, *Veech I*, and *Veech II*, are clearly deficient with respect to the claimed invention. At a minimum, nowhere do these references disclose or suggest the carbon dioxide partial pressure features, let alone the carbon dioxide partial pressure features combined with the additional other features, such as the unique combination of two buffers(bicarbonate and a weak acid), to provide a biochemically balanced peritoneal dialysis solution capable of correcting metabolic acidosis as required by the claimed invention. Indeed, the Patent Office even admits that these references fail to disclose the carbon dioxide partial pressure features of the claimed invention.

Even if combinable, Appellants do not believe that the Patent Office can rely on *Zander* solely to remedy the deficiencies of the claimed invention. As previously discussed, Appellants believe that *Zander* effectively teaches away from the claimed invention. For example, the specific composition in *Zander* as disclosed in column 2 is without a weak acid component. Further, the

composition disclosed in column 6 of *Zander* requires a weak acid concentration in the form of acetate that is too high and dangerous to use, whether acetate and/or other weak acids are employed at this concentration. Indeed, the peritoneal dialysis solutions as defined by Claim 1, 6 and 10 do not include acetate as a weak acid. Again, Appellants' position with respect to *Zander* is supported by the Declaration of Dr. Leo Martis as discussed above. See, Exhibit R.

What the Patent Office clearly has done is to apply hindsight reasoning to justify the obviousness rejections. Of course, this is not proper. The Federal Circuit has held that "[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Associates, Inc. v. Garlock, Inc.* 220 U.S.P.Q. 303, 312-313 (Fed. Cir. 1983). Indeed, the claimed peritoneal dialysis solutions provide a unique combination of two buffers (bicarbonate and a weak acid, such as selected from a group that does not include acetic acid) in combination with a specified level of carbon dioxide partial pressure which is both safe and effective in maintaining an acid-base balance in peritoneal dialysis patients. The safety and the efficacy of the solution of the present invention is established by the data presented in the Declaration of Dr. Martis. See, Exhibit F, *Martis* Declaration, ¶¶ 7-10.

Again, *Schambye, Veech I* and *Veech II* are clearly deficient with respect to the claimed peritoneal dialysis solutions as previously discussed. Further, *Zander* cannot be relied on solely to remedy the deficiencies of same. Indeed, *Zander* effectively teaches away from the claimed invention as previously discussed. In view of same, Appellants do not believe that one skilled in the art would be inclined to modify the cited art to arrive at the claimed invention. Therefore, Appellants believe that the cited art, even if combinable, fails to render obvious the claimed invention.

Accordingly, Appellants respectfully request that the rejections under 35 U.S.C. § 102 and § 103 be reversed.

IX. CONCLUSION

Appellants' claimed invention set forth in claims 1-16 is neither taught nor suggested by the cited references, either alone or in combination. The Patent Office has failed to establish a *prima facie* case of anticipation and obviousness with respect to the rejection of the claimed invention. Accordingly, Appellants respectfully submit that the anticipation and obviousness rejections are erroneous in law and in fact and should therefore be reversed by this Board.

Respectfully submitted,

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APPENDIX

1. A peritoneal dialysis solution including bicarbonate at a level of less than or equal to 30 mM/L, having a carbon dioxide partial pressure that is less than 60 mmHg and including at least one weak acid at a level of between approximately 15 mEq/L and approximately 20 mEq/L selected from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate.

2. The peritoneal dialysis solution of Claim 1 wherein bicarbonate is present in the solution at 25 mM/L.

3. The peritoneal dialysis solution of Claim 1 wherein the carbon dioxide partial pressure of the solution is approximately the same as the carbon dioxide partial pressure of blood.

4. The peritoneal dialysis solution of Claim 1 wherein the solution has a pH of approximately 7.0 to about 7.4.

5. The peritoneal dialysis solution of Claim 1 wherein the weak acids have a pKa of < 5.0.

6. A peritoneal dialysis solution comprising:

Dextrose (hydrous) (g/dl)	1.5-4
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4
Magnesium (mEq/L)	0.0-4
Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-2

wherein the weak acid is at least one acid chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate, the solution having a carbon dioxide partial pressure that is less than 60 mmHg.

7. The peritoneal dialysis solution of Claim 6 wherein the solution has a pH of approximately 7.0 to about 7.4.

8. The peritoneal dialysis solution of Claim 6 wherein the weak acids have a pKa of < 5.0.

9. The peritoneal dialysis solution of Claim 6 wherein the carbon dioxide partial pressure of the solution is approximately the same as the carbon dioxide partial pressure of normal blood.

10. A peritoneal dialysis solution comprising:

Dextrose (hydrous) (g/dl)	1.5-4.2
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0
Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-20

wherein the weak acid is at least one acid chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate, and the solution has a carbon dioxide partial pressure that is substantially similar to the carbon dioxide partial pressure of a normal subject's blood and the solution has a pH of approximately 7.0 to about 7.4.

11. A method for correcting metabolic acidosis in a dialysis patient suffering or likely to suffer from same comprising the step of:

administering to a patient a peritoneal dialysis solution that has a bicarbonate level and carbon dioxide partial pressure that are substantially similar to that found in the patient's blood wherein the solution comprises:

Dextrose (hydrous) (g/dl)	1.5-4
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4
Magnesium (mEq/L)	0.0-4
Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-2

12. The method of Claim 11 including the step of administering to the patient a weak acid that is present in the solution in an amount that offsets the daily hydrogen production of approximately 1 mEq/kg/day.

13. The method of Claim 12 wherein the weak acids have a pKa of < 5.0.

14. The method of Claim 10 wherein the solution has a pH of approximately 7.0 to about 7.4.

15. The method of Claim 11 wherein the solution does not include lactate.

16. The method of Claim 12 wherein the weak acid is present in the solution at a level of approximately 10 to about 20 mEq/L.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,248	09/17/2001	Leo Martis	DI-4641 CONT	8992

PJK

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OIPE JC79 AUG 11 2003 PATENT & TRADEMARK OFFICE

EXAMINER
KEYS, ROSALYND ANN

ART UNIT	PAPER NUMBER
1621	12

DATE MAILED: 01/14/2003

DUE: 4-14-03

Please find below and/or attached an Office communication concerning this application or proceeding.

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CASE DI 4641 Cont
DKT. DATE 3/14 SEEN BY ATTY. ____
1/20/03 FINAL DATE 4/14 RESP. SENT 4/5
SUBJECT Response Due OA Final

Office Action Summary	Application No. 09/955,248	Applicant(s) MARTIS ET AL.	
	Examiner Rosalynd Keys	Art Unit 1621	

The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

1. Claims 1-16 are pending.

Claims 1-16 are rejected.

Information Disclosure Statement

2. The information disclosure statement filed October 28, 2002 has been considered .

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 2, and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Schambye et al. (Peritoneal Dialysis International, Vol. 13, Supplemental 2, October 1992, pp. S116-S118) in view of Zander (US Patent No. 5,296,242), for the reasons given in the previous office action, Paper No. 9.

5. Claims 1, 2, and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Veech (US 4,663,166) in view of Zander (US Patent No. 5,296,242), for the reasons given in the previous office action, Paper No. 9.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schambye et al. (Peritoneal Dialysis International, Vol. 13, Supplemental 2, October 1992, pp. S116-S118) in view of Zander (US Patent No. 5,296,242), for the reasons given in the previous office action, Paper No. 9.

9. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Veech et al. (US 4,663,166) in view of Zander (U.S. Patent No. 5,296,242), for the reasons given in the previous office action, Paper No. 9.

10. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Veech (US 6,020,007) in view of Zander (US 5,296,242), for the reasons given in the previous office action, Paper No. 9.

Response to Arguments

Rejection of claims 1, 2, and 4-8 under 35 U.S.C. 102(b) as being anticipated by Schambye et al. (Peritoneal Dialysis International, Vol. 13, Supplemental 2, October

1992, pp. S116-S118) in view of Zander (US Patent No. 5,296,242) and claims 1, 2, and 4-8 under 35 U.S.C. 102(b) as being anticipated by Veech (US 4,663,166) in view of Zander (US Patent No. 5,296,242)

11. Applicant's arguments filed October 28, 2002 have been fully considered but they are not persuasive.

Applicants argue that as a matter of law, anticipation requires the disclosure in a *single (emphasis added)* prior art reference of each element of the claim under consideration. This argument is not persuasive because normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure; "

(B) Explain the meaning of a term used in the primary reference; or

(C) Show that a characteristic not disclosed in the reference is inherent.

In the instant case multiple references are being used to show that a characteristic not disclosed in the reference is inherent. In particular, Zander is combined with Schambye et al. to show that the claimed carbon dioxide partial pressure is inherently taught by Schambye et al.

The Applicants further argue that even if the anticipation rejections are not considered improper as a matter of law, applicants respectfully submit that the cited references fail to disclose a number of features of the claimed invention. The Examiner

disagrees. The cited references do teach each and every element of the claimed invention, which is pointed out in the previous office action, Paper No. 9.

For the above reasons, the rejection of claims 1, 2, and 4-8 under 35 U.S.C. 102(b) as being anticipated by Schambye et al. in view of and the rejection of claims 1, 2, and 4-8 under 35 U.S.C. 102(b) as being anticipated by Veech in view of Zander are maintained.

Rejection of claims 1- under 35 U.S.C. 103(a) as being unpatentable over Schambye et al. (Peritoneal Dialysis International, Vol. 13, Supplemental 2, October 1992, pp. S116-S118) in view of Zander (US Patent No. 5,296,242; Rejection of claims 1-16 under 35 U.S.C. 103(a) as being unpatentable over Veech et al. (US 4,663,166) in view of Zander (U.S. Patent No. 5,296,242; and rejection of claims 1-16 under 35 U.S.C. 103(a) as being unpatentable over Veech (US 6,020,007) in view of Zander (US 5,296,242

The Applicants argue that the primary references are clearly deficient with respect to the claimed invention. The Examiner disagrees for reasons given in the previous office actions.

The bulk of the Applicants' arguments are directed to the Zander reference. The applicants argue that while Zander does teach a dialysis solution with a carbon dioxide partial pressure of about 40 mmHg, a person skilled in the art of peritoneal dialysis would readily recognize that the solutions proposed by Zander would not be effective in maintaining the acid-base balance of dialysis patients. This argument is not persuasive because 1) it is not the solution of Zander that the instant claims are found

to be unpatentable, but the solution that results as a combination of the primary references with the carbon dioxide partial pressure disclosed by Zander (see previous office action, Paper No. 9); and 2) Zander teaches that by using carbon dioxide partial pressures that correspond to physiological blood plasma (40 mm Hg) one can prevent alkalosis or acidosis from occurring (see column 2, lines 35-54).

With regard to the Applicants arguments that the preferred weak acid of Zander is clearly acetic acid/acetate, the Examiner wishes to remind the applicants that it is well established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches to a person of ordinary skill in the art. *In re Boer*, 355 F.2d 961, 148 USPQ 507 (CCPA 1966); *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 279, 280 (CCPA 1976); *In re Fracalossi*, 681 F.2d 792, 794, 215 USPQ 569, 570 (CCPA 1982); *In re Kaslow*, 707 F.2d 1366, 1374, 217 USPQ 1089, 1095 (Fed. Cir. 1983). In the instant case, Zander clearly suggests the use of other weak acids, including the claimed weak acids, which are also taught by the primary references.

Any further arguments with regard to Zander teaching the use of acetic acid/acetate will not be addressed by the Examiner because the rejection is not based on the use of acetic acid/acetate as taught by Zander, but on the combination of Zander with the primary references, as mentioned above. It is this combination of references that the applicants' invention has failed to patentably distinguish over. Further, it has been held that one cannot show non-obviousness by attacking references individually

where, as here, the rejections are based on combinations of references. *In re Keller*, 208 USPQ 871 (CCPA 1981).

In response to Applicants' arguments that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the invention was made, and does not include knowledge gleaned only from the applicants' disclosure, such a reconstruction is proper. *In re McLaughlin*, 443 F.2d 1392; 170 USPQ 209 (CCPA 1971). In the instant case, all elements of the claimed invention are disclosed by the cited references. There is no element or part of Applicants' claimed invention, which is not suggested or specifically disclosed. The motivation to combine the teaching of the references is found in column 2, lines 35-54 of Zander.

The Applicants' argue that the Examiner's conclusion of obviousness is based upon an "obvious to try" rationale. The Examiner disagrees because the cited references disclose the use of each of the claimed elements in a peritoneal dialysis solution as well as the reason or motivation for using the claimed amounts of each of the elements.

The Applicants' argue that Zander teaches away from its combination with the cited primary references. The Examiner disagrees. In column 3, lines 62-68 Zander teaches that the inventive solutions contain the immediate buffer bicarbonate in physiological concentration, together with the long-term buffer metabolized anion in the

desired concentration. Preferred metabolizable acids useable in the aqueous solutions according to the invention are pyruvic, lactic, oxalic, fumaric, acetic, malic, maleic, malonic and succinic acids. The solution disclosed in Schambye et al. contain bicarbonate and lactate. The solutions disclosed in Veech '166 and Veech '007 contain bicarbonate with pyruvate and/or lactate. Thus, the possible dialysis solutions disclosed by Zander correspond to the dialysis solutions, which are disclosed by the primary references. What is lacking in the primary references is a specific teaching to use physiological carbon dioxide partial pressures, i.e., a carbon dioxide partial pressure of 40 mmHg. Zander teaches using a physiological carbon dioxide partial pressure. The reason to use such pressure has been given above, as well as in the previous office action, Paper No. 9.

The Examiner believes a prima facie case of obviousness has been shown. Thus, for the above reasons the rejections under 35 USC 103(a) are maintained.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosalynd Keys whose telephone number is 703-308-4633. The examiner can normally be reached on M and F 3:00-8:00 pm and T-R 5:30-10:30 am.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Rosalynd Keys
Primary Examiner
Art Unit 1621

R. Keys
January 10, 2003

Applicants' Copy

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SUPPLEMENTAL INFORMATION DISCLOSURE CITATION IN AN APPLICATION (Use several sheets if necessary) PTO Form 1449	Atty Docket No. DI-4641 CON.	Application No. 09/955,248
	Applicant Martis et al.	
	Filing Date Sept. 17, 2001	Group 1621

U.S. PATENT DOCUMENTS

Examiner's Initials		Document Number	Publication Date	Inventor	Class	Subclass	Filing Date If Appropriate
		~~EP0613688~~	~~09-07-94~~	~~Europe~~			
		~~FR2753099~~	~~03-13-98~~	~~France~~			
		~~EP0935967~~	~~03-13-98~~	~~Europe~~			

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FOREIGN PATENT DOCUMENTS

Examiner's Initials		Document Number	Publication Date	Country	Class	Subclass	Translation Yes	Translation No
RK		EP0613688	09-07-94	Europe	—	—		
RK		FR 2753099	03-13-98	France	—	—		
RK		EP0935967	03-13-98	Europe	—	—		

Examiner's Initials		**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*

Examiner: R. Key	Date Considered: 1/9/03

*Examiner: Initial if citation considered, whether or not citation is in conformance with PEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PD in the 90's. Selected Topics of the VIth ISPD Congress
October 1 - 4, 1992. Thessaloniki, Greece
Peritoneal Dialysis International. Vol. 13. Supplement 2

0896-8608/93 $3.00 + .00

THE CYTOTOXICITY OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS SOLUTIONS WITH DIFFERENT BICARBONATE/LACTATE RATIOS

Hans Thalsgård Schambye,[1] Fritz Bangsgaard Pedersen,[2] Hanne Knoldsborg Christensen,[3] Henrik Berthelsen,[4] and Palle Wang[1]

Departments of Clinical Chemistry[1] and Nephrology,[2] and The Hospital Pharmacy,[3] Odense University Hospital, and The Institute of Pharmacology,[4] Odense University, Odense, Denmark

Five different bicarbonate-based continuous ambulatory peritoneal dialysis (CAPD) solutions (pH: 7.0–7.4; bicarbonate: 10–27 mM; lactate: 20.8–6.7 mM) were produced in order to examine the cytotoxic effects of the different compositions. The migratory capacity of normal human polymorphonuclear (PMN) granulocytes after exposure to the solutions was used as a cytotoxicity assay.

All the tested solutions reduced cellular function compared to a standard cell culture medium, but considerable differences between the solutions were observed.

The optimal conditions for the PMN migration were at a pH of 7.0 and at bicarbonate and lactate concentrations f 20 mM and 12.5 mM, respectively. Bicarbonate concentrations of more than 25 mM were associated with reduced cellular function as were lactate concentrations of more than 15 mM.

The most advantageous CAPD solution regarding cytotoxicity towards normal human PMN's is a combination f a lactate and bicarbonate-based solution, which has a bicarbonate concentration of approximately 20 mM, a lactate concentration of 12.5 mM, and a pH of approximately 7.2.

KEY WORDS: Neutrophils; bicarbonate; lactate; pH; cytotoxicity.

Several studies have demonstrated that continuous ambulatory peritoneal dialysis (CAPD) solutions and effluents are cytotoxic (1-3). The cytotoxicity of the commercially available dialysis solutions is due to a low pH (5.0–5.5), hypertonicity, lack of potassium, and a high concentration of lactate (30–40 mM) (1-4).

The cytotoxicity may impair the function of the immunoactive cells in the peritoneal cavity during dialysis and may thereby contribute to the development of peritonitis (3,5). The use of bicarbonate as a buffer base has been advocated in order to allow an increase of the pH and a decrease of the lactate concentration of the solutions (1,4). The hypertonicity cannot be decreased and potassium not added without hampering the dialysis efficacy of the solutions.

Bicarbonate solutions are less cytotoxic than lactate solutions *in vitro* (1,2). Examination of the cytotoxicity of dialysis effluents obtained after treatment with lactate and bicarbonate-based solutions indicated that the biocompatibility of the bicarbonate-based solutions could be improved by decreasing the bicarbonate concentration (3).

The aim of the present study was to examine the impact of different pH and bicarbonate and lactate concentrations on the cytotoxicity of CAPD solutions and to propose a new composition for dialysis solutions that is less cytotoxic.

METHODS

Dialysis Solutions: Five bicarbonate-based solutions prepared by The Hospital Pharmacy, Odense University Hospital, Odense, Denmark, were examined. The compositions of the solutions are listed in Table 1.

Polymorphonuclear Granulocytes (PMN): PMN's were isolated from heparinized venous blood of healthy donors by density gradient centrifugation on Polymorphprep (Nycomed AS, Oslo, Norway), washed twice in RPMI 1640 (Gibco, Paisley, Scotland), counted on an automatic cell counter (Sysmex NE 8000, Toa Medical Instruments, Tobe, Japan), and resuspended in the fluid to be tested or in RPMI 1640, which served as a reference medium, at a standard cell concentration (10^6 cells/mL). More than 98% of the cells were PMN's. All examinations were carried out in a 5% (40 mmHg) CO_2 atmosphere.

Migration Assay: The migration of the PMN's in micropore membranes was measured. A micropore membrane (Sartorius 3μ, Goettingen, Germany) was placed on a filter layer containing casein, a

Correspondence to: F. B. Pedersen, Department of Nephrology, Odense Univ rsity Hospital, Sønder Boul vard 29, DK5000 Odense C, Denmark.

TABLE 1
The pH and Concentration of Bicarbonate, Pyruvate, and Lactate of the Different Bicarbonate-Based Dialysis Solutions. Other c nstituents were (in mM): Glucose 77.8, Cl^- 101.5, Na^+ 130, Ca^{2+} 1.75, Mg^{2+} 0.5, Citrate 1.4; d-β-hydroxybutyrate 2; Osmolarity 350 mOsm/L.

Composition of Bicarbonate-Based Solutions					
Substanc (mM)	91a	91b	91c	91d	91e
Pyruvate	4.2	3.3	2.5	3.0	1.3
Lactate	20.8	16.7	12.5	15.0	6.7
icarbonate	10.0	15.0	20.0	17.0	27.0
pH	7.0	7.0	7.0	7.2	7.4

chem attractant. Twelve-millimeter plastic caps (Nunc, Roskilde, Denmark) were filled with the cell suspension and inverted onto the membrane. The migrated distance was measured microscopically by the "leading front" method after 30 minutes of incubation. Details concerning the applied methods are given elsewhere (2).

Intracellular pH Measurement: The PMN's were dyed with BCECF–AM (5μM) for 60 minutes, washed twice in Hanks–Hepes (Gibco, Paisley, Scotland), transferred to cuvettes, and resuspended in the solution to be tested. The fluorescence of the cell suspension was measured at excitations of 505 and 439 nm and an emission of 545 nm. A ratio of the two measurements was calculated. Calibration was carried out by suspending the cells in a saline solution (144 mM KCl, 10 mM Hepes, 10μM Nigericin), in which the intracellular pH (pH_i) is identical to the extracellular pH (pH_e). Fluorescence ratios at five different pH_e/pH_i between 6.8 and 7.5 were measured, and a linear regression curve for these measurements was calculated. By means of this curve the pH_i of the cells in the test solutions was estimated.

STATISTICAL ANALYSES

Data were evaluated with Student's t-test, one-way analysis of variance (ANOVA), and linear regression. Confidence intervals were determined by the t distribution. Statistical significance was accepted at $p<0.05$. All data on migration are given as percentages of simultaneously measured results in RPMI 1640. This eliminates the intraindividual and interindividual variances of the donors (2).

RESULTS

Migration: Examination of the effect of different bicarbonate, lactate, and pyruvate concentrations on cell function (Figure 1) revealed that all the CAPD solutions inhibited PMN function compared to RPMI 1640. Soluti ns with a low-bicarbonate and a high-lactate and pyruvate concentration (91a, 91b, and 91d) and the solution with high-bicarbonate and low-lactate/pyruvate concentrations (91e) inhibited the PMN function the most, whereas 91c with a bicarbonate concentration of 20 mM, a lactate concentration of 12.5 mM, and a concentration of pyruvate of 2.5 mM was the least inhibitory solution.

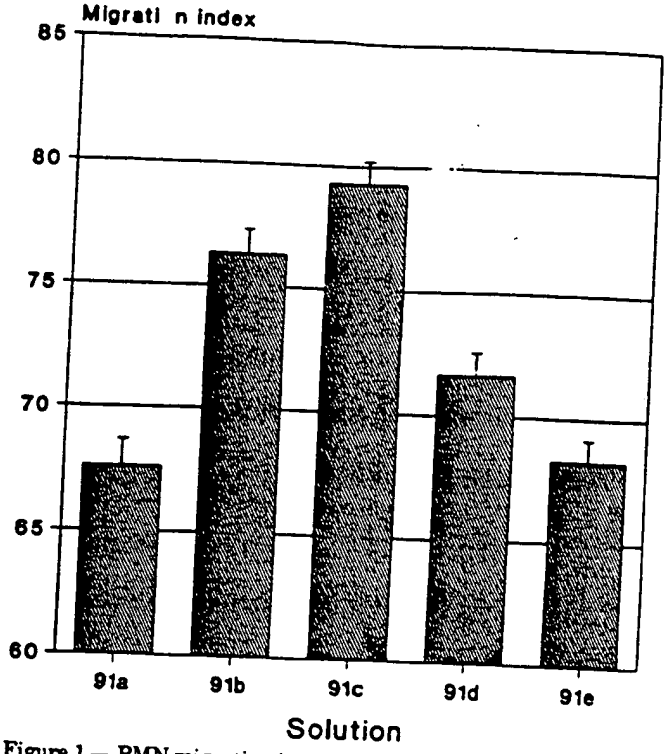

Figure 1 — PMN migration (mean) after exposure to the different bicarbonate-based CAPD solutions. PMN from two donors were used. The error bars indicate an 80% confidence interval of the mean. Data are given as percentages of values obtained simultaneously in RPMI 1640.

There was a considerable difference between 91c and 91d concerning their impact on the cellular function in spite of limited differences in bicarbonate concentration and pH (Table 1 and Figure 1).

Intracellular pH: The pH_i of the PMN's was 6.96 (6.82–7.10) (mean 95% confidence interval) after exposure to the bicarbonate-based solutions compared to 7.03 (6.87–7.19) in Hanks–Hepes. It was thus not possible to demonstrate any difference in pH_i following incubation of PMN's in the different CAPD solutions.

DISCUSSION

Bicarbonate has been advocated as a buffer base by several authors to improve the biocompatibility of CAPD solutions (4,6).

Our examinations of the cytotoxicity of 87b, a bicarbonate-based solution (pH 7.4, lactate 5 mM, bicarbonate 29 mM), demonstrated that the solution was less toxic than the commercially available dialysis solutions, but the solution was cytotoxic nevertheless (1-3). Further examinations indicated that the

cytotoxicity was partly due to a too high bicarbonate concentration (3).

These observations are supported by the present study, which demonstrated that a solution with a pH of 7.0, a lactate concentration of 12.5 mM, and a bicarbonate concentration of 20 mM is less cytotoxic than solutions with either higher lactate or higher bicarbonate concentrations (Figure 1 and Table 1).

The inhibitory effect of high-bicarbonate concentrations on cell function could be due to intracellular acidification (7). Extracellular bicarbonate is at equilibrium with CO_2, which diffuses much more easily through the cell membrane than the ionized bicarbonate. In the cytosol, CO_2 forms carbonic acid after reaction with water leading to a reduction of the intracellular pH.

We could not demonstrate any difference in pH_i of the PMN's after exposure to the different solutions. The applied method was, however, quite unstable as demonstrated by the variance of the reference pH_i, and it was difficult to keep the solutions under the appropriate 5% CO_2 atmosphere during measurement. Consequently, we cannot conclude that a high extracellular bicarbonate concentration does not decrease pH_i, or that the observed differences in cytotoxicity were not due to differences in pH_i.

On the other hand, we cannot rule out that the observed differences in cytotoxicity were caused by unknown effects of unbalanced extracellular lactate/bicarbonate ratios.

The considerable difference in cytotoxicity between 91c and 91d cannot be explained by differences in pH or bicarbonate concentration. Consequently, the higher toxicity of 91d must be due to the higher concentration of lactate and/or pyruvate.

CONCLUSION

The present results indicate that the most advantageous CAPD solution regarding cytotoxicity towards normal human PMN's is a combination of a lactate and a bicarbonate-based solution, which has a bicarbonate concentration of approximately 20 mM, a lactate concentration of approximately 12.5 mM, and a pH of approximately 7.0.

ACKNOWLEDGMENT

The authors wish to express their gratitude to laboratory assistant Inge Jakobsen, who carried out the migration and pH_i analyses.

The present study was supported by grants from the Danish Medical Research Council and from Odense University.

REFERENCES

1. Kristensen SR, Pedersen FB. Bicarbonate versus lactate based continuous ambulatory peritoneal dialysis fluids. Cytotoxicity testing in a model system of quiescent fibroblasts. *Nephrol Dial Transplant* 1993; 8:163-7.
2. Schambye HT, Pedersen FB, Wang P. Cytotoxicity of continuous ambulatory peritoneal dialysis (CAPD) solutions. A biocompatibility study applying human polymorphonuclear granulocytes rather than laboratory animals. *Alternatives Lab Anim* 1992; 20:275-9.
3. Schambye HT, Pedersen FB, Wang P. Bicarbonate is not the ultimate answer to the biocompatibility problems of CAPD solutions: a cytotoxicity test of CAPD solutions and effluents. *Adv Perit Dial* 1992; 41-6.
4. Veech RL. The toxic impact of parenteral solutions on the metabolism of cells: a hypothesis for physiological parenteral therapy. *Am J Clin Nutr* 1986; 44:519-50.
5. Keane WF, Peterson PK. Host defense mechanisms of the peritoneal cavity and continuous ambulatory peritoneal dialysis. *Perit Dial Bull* 1984; 3:122-7.
6. Feriani M, La Greca G. CAPD with bicarbonate solution. *Adv Exp Med Biol* 1989; 260:139-47.
7. Kildeberg P. Quantitative acid-base physiology. Odense, Denmark: Odense University Press, 1981.

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United States Patent [19]

Zander

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[54] AQUEOUS SOLUTION AND THE USE THEREOF

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[21] Appl. No.: 922,819

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[30] Foreign Application Priority Data

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[51] Int. Cl.[5] A61K 33/10

[52] U.S. Cl. 424/717; 424/715

[58] Field of Search 424/717, 715

[56] References Cited

U.S. PATENT DOCUMENTS

4,489,535	12/1984	Veltman	424/717
4,548,817	10/1985	Filley et al.	424/717
4,604,286	8/1986	Kawajiri	424/717

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[57] ABSTRACT

A sterilizable aqueous solution with substantially physiological values of the pH, bicarbonate concentration and CO_2 partial pressure, as well as with metabolizable anions in the form of two separately stored single solutions, which are combined with one another prior to use and whereof one is a bicarbonate-free, acid solution and the other a bicarbonate-containing, alkaline solution, is characterized in that per liter of the finished solution obtained by combining the two single solutions, the acid single solution contains 7.3 mmole±3% of at least one metabolizable, organic acid and the alkaline single solution 19.1 mmole±3% of alkali bicarbonate and 6.1 mmole±3% of alkali carbonate.

7 Claims, No Drawings

AQUEOUS SOLUTION AND THE USE THEREOF

Bicarbonate-containing dialysis, substitution or infusion liquids for hemodialysis, peritoneal dialysis, hemofiltration or infusion are already known. Such bicarbonate-containing liquids lead to various galenic problems, particularly if they are not used immediately after preparation and are instead stored in containers.

Bicarbonate solutions are not stable, because there is always a risk that CO_2 escapes from a bicarbonate solution and consequently the composition of the solution changes. Certain constituents of such liquids, particularly glucose and amino acids, can only be sterilized or stored with acid pH-values in the range 5.0 to 5.5, because otherwise denaturation and/or brown colouration occurs. However, to be usable, dialysis or infusion solutions must be sterilizable. For the compensation of calcium losses, it is often necessary to supply calcium ions to dialysis patients with the dialysis solution. However, such calcium ions cannot be brought together at an alkaline pH-value with the carbonate ions, which can be formed from the bicarbonate, because otherwise insoluble calcium carbonate would precipitate.

EP-OS 161 471 discloses a two-chamber container for the storage and preparation of a bicarbonate-containing dialysis, substitution or infusion liquid, which is made from a special polymer, which separates the two chambers from one another in a liquid and gas-tight manner. One chamber contains a bicarbonate-free acid solution and the other a bicarbonate-containing alkaline solution. Prior to use the two chambers can be interconnected for mixing the contents and by means of an outlet tube the mixed solution can be supplied for its intended use.

However, the latter document does not describe the simultaneous use of alkali carbonate and alkali bicarbonate. It is in fact expressly pointed out that one of the two alkali salts is to be used. The storage container provided for such liquids is difficult and expensive to manufacture, because it must be ensured that no CO_2 escapes, so that the composition of the bicarbonate-containing alkaline solution does not change during storage.

The aqueous solutions described in EP-OS 161 471 do not have physiological values of the pH, the bicarbonate concentration and the CO_2 partial pressure. The same applies with regards to the dialysis solutions described in EP-OS 277 868. The dialysis solutions used up to now, particularly in continuous ambulatory peritoneal dialysis do not have a physiological composition, but instead, for stability reasons, always an acid pH-value, such as in the range 5.2 to 5.5. Such acid dialysis solutions can lead to damage to the peritoneum, to irritation of the defence system of the body and to pain in the abdominal cavity.

DE-OS 3 514 346 discloses liquids, particularly for the calibration of CO_2 analysis equipment, which in contact with the atmospheric air do not change their overall CO_2 content and which contain certain concentrations of alkali carbonate and alkali bicarbonate. However, in the case of these solutions it is solely a question of obtaining a liquid with a CO_2 partial pressure, which corresponds to that of atmospheric air, but no attempt is made to adjust physiological values of the acid—base status of said liquid.

The problem of the invention was to obtain a sterilizable, aqueous solution with physiological values of the pH, bicarbonate concentration and CO_2 partial pressure usable as a dialysis, substitution or infusion solution and which can be stored in air, without requiring special equipment for preventing a diffusing off or in of carbon dioxide.

According to the invention this problem is solved by an aqueous solution, which contains metabolizable anions and which is in the form of two separately stored single solutions to be combined prior to use, whereof one is a bicarbonate-free, acid solution and the other a bicarbonate-containing, alkaline solution, the aqueous solution according to the invention being characterized in that per liter of the finished solution obtained by combining the two single solutions, the acid single solution contains 7.3 mmole±3% of at least one metabolizable organic acid and the alkaline single solution 19.1 mmole±3% alkali bicarbonate and 6.1 mmole±3% alkali carbonate.

Aqueous solutions according to the invention having such a composition can be stored in air, without having to be placed in special containers preventing a diffusing off or in of CO_2. Thus, there is no need to use as storage containers either glass bottles or flasks, which in many cases are difficult to handle, or specially constructed gas-impermeable containers, such as are e.g. described in EP-OS 161 471. This advantage is e.g. particularly significant in the case of ambulatory peritoneal dialysis, in which it is comfortable and advantageous for the patient to be able to use a normal bag for the dialysis liquid and to be independent of glass containers.

The solutions according to the invention are sterilizable, even if they contain e.g. glucose or amino acids, because the acid, bicarbonate-free solution has a pH-value of approximately 5, which prevents denaturation or brown colouration.

The preliminary research leading to the present invention revealed that dialysis, substitution or infusion solutions are particularly suitable if their pH-value, bicarbonate concentration and CO_2 partial pressure corresponds to the physiological blood plasma values. These physiological values of the acid-base status are in the case of the pH value 7.40±0.05, for the bicarbonate concentration 24 mmole/l and for the CO_2 partial pressure 40 mm Hg. If these values are obtained in an artificially prepared aqueous solution, then on using such solutions as a dialysis, substitution or infusion solution, it is ensured that there is not overdosing or underdosing relative to the acid-base status and consequently an alkalosis or acidosis is produced, that no hyperventilation or hypoventilation occurs with respect to the breathing of a patient and at the point of application when used as an infusion solution there are no local reactions on the vein or when used as a peritoneal dialysis solution there are no local reactions on the peritoneum.

The inventive aqueous solutions quantitatively give said physiological values, so that the indicated advantages are obtained when using said aqueous solutions.

The aqueous solutions according to the invention also permit the addition of all possible desired electrolytes, such as calcium and/or magnesium ions, without there being any risk of precipitating calcium or magnesium carbonate, because these ions are added to the bicarbonate-free acid solution.

Metabolizable anions of organic acids are desired for the therapy of acidosis. In the inventive aqueous solutions these anions constitute long-term buffers, because their action is only observed after minutes to hours following administration, as a function of the reaction in

the hepatic metabolism and as a function of the organic acid or acids used.

This long-term buffer effect supplements the immediate buffer effect of the bicarbonate in physiological concentration.

On combining the two single solutions, accompanied by the formation of the finished inventive solution, the metabolizable, organic acids of the acid single solution primarily quantitatively react with the carbonate ions of the alkaline single solution, because the carbonate ions have a higher pK than the bicarbonate ions. From the carbonate ions are formed bicarbonate ions, which only react in a secondary, quantitative manner with the remaining metabolizable organic acids, accompanied by the formation of CO_2+H_2O. This secondary reaction produces a CO_2 partial pressure of 40 mm Hg.

In particular the alkali carbonate, but also alkali bicarbonate are used in the solution system according to the invention in order to form the alkali salts of the added, metabolizable organic acids, which is decisive for the therapy. If the organism was in fact supplied with the organic acid, such as e.g. lactic acid, the latter dissociates completely at the physiological pH of 7.40 and consequently leads to acidosis. If it is decomposed in the metabolism, such as in the liver, CO_2+H_2O are formed, i.e. neutral end products. In the case of lactic acid infusion, e.g. the pH-value immediately drops (acidosis) and is then standardized within roughly 2 hours.

However, if the alkali salt, such as sodium lactate is added to the organism, within minutes to hours and in accordance with the metabolism of the acid salt in the liver, there is an alkalization of the organism, because per mole of salt the alkali salt carries 1 mole H^+ into the metabolism. In the case of a lactate infusion, e.g. the pH-value initially remains neutral and then e.g. within 2 hours passes into the alkaline range.

The speed at which a metabolizable anion leads to an alkalization of the organism is dependent on the metabolic position of the liver, the nature of the anions supplied and the anion concentration.

Metabolizable, organic anions are added to the infusion solutions, in order to prophylactically initiate an alkalization of the organism. Metabolizable, organic anions are also used in dialysis solutions, in order to compensate the acidosis of the dialysis patient which increases during dialysis.

Up to now, for galenic reasons no infusion solution has contained bicarbonate, which must necessarily lead to a so-called dilution acidosis, because per liter of solution the organism must make available from its reserve 24 mmole of bicarbonate. This dilution acidosis can be detected both in vitro and in vivo.

The solutions according to the invention offer the further advantage that with respect to the metabolizable ions, whose alkalization effect is desired, no false dosing is possible, which can in turn lead to an iatrogenic alkalosis, which may represent a risk for the patient, because he must compensate this alkalosis by hypoventilation, which is limited because the reduction of breathing can produce a hypoxia (oxygen deficiency) on the part of the patient.

Thus, the inventive solutions contain the immediate buffer bicarbonate in physiological concentration, together with the long-term buffer metabolized anion in the desired concentration. Preferred metabolizable acids usable in the aqueous solutions according to the invention are pyruvic, lactic, oxalic, fumaric, acetic, malic, maleic, malonic and succinic acids.

It is also preferable to adjust the divergences of 7.3 mmole f the metabolizable acids, 19.1 mmole of the alkali bicarbonate and 6.1 mmole of the alkali carbonate per liter of finished solution to only ±1%, in order to obtain a pH-value of 7.40±0.05 and obtain divergences of the CO_2 partial pressure of ±4 mm Hg.

The above-indicated millimole quantitities for the individual components relate to the volume of the finished solution obtained from the two single solutions by mixing, so that the volumes of the acid and alkaline single solutions can be varied at random, provided that their concentrations are adjusted in accordance with the above teaching. If e.g. the acid and alkaline single solution is in each case adjusted to 1 liter, so that the finished solution has a volume of 2 l, then in the acid solution it is necessary to have 14.6 mmole/l of the metabolizable, organic acid and in the alkaline solution 38.2 mmole/l of alkali bicarbonate and 12.2 mmole/l of alkali carbonate. On changing the volume ratios of the two single solutions the concentrations must be correspondingly converted.

When the description and claims refers to an acid and alkaline single solution, this obviously also covers the possibility of the total volume of the acid and alkaline single solution being subdivided, which however, normally leads to no additional advantage. These partial quantities of the alkaline or acid single solution can be the same or different with respect to the composition, provided that in all the partial quantities of the single solutions together the above-indicated millimoles of the indicated components are obtained.

It is also appropriate for the acid single solution to additionally contain calcium and magnesium ions. As stated, it can also additionally contain other substances, such as glucose and/or amino acids.

The aqueous solutions according to the invention completely eliminate the hitherto known problems of bicarbonate infusions. When administering bicarbonate for the therapy of an acidosis CO_2+H_2O. The administration of relatively high bicarbonate concentrations consequently always leads to a hyperventilation, which is unpleasant for the patient, because the necessarily formed CO_2 represents a breathing stimulus, which triggers the hyperventilation, for the purpose of breathing the additionally formed CO_2. As the inventive infusion solutions have a bicarbonate concentration of 24 mmole/l, the overdosing or incorrect dosing of bicarbonate in an infusion solution is automatically excluded.

The acid single dose can, in addition to the metabolizable organic acid or acids, also contain salts thereof, in order to obtain the desired metabolizable anion concentration.

The following tables I to III provide examples for the composition of the acid single solution in conjunction with the resulting base concentrations in the finished, combined solution following 1:1 mixing with the alkaline solution, all the details relating to 37° C. and the concentrations are given in millimole/liter.

TABLE I

Single solutions, pH = 4.0 to 6.0
Examples of the composition of the acid single solutions and the base concentrations in the finished solutions (details based on 37° C., concentrations (c) in mmole/l)

			Acid Single Solution			Finished Solution
Acid	Base	pK	pH	cAcid	cBase	cBase
Lactic acid	Lactate	3.678	4.0	14.60	30.65	22.62
Oxalic acid	Oxalate	3.846	4.0	14.60	20.82	17.71

TABLE I-continued

Single solutions, pH = 4.0 to 6.0
Examples of the composition of the acid single solutions and the base concentrations in the finished solutions (details based on 37° C., concentrations (c) in mmole/l)

			Acid Single Solution			Finished Solution
Acid	Base	pK	pH	cAcid	cBase	cBase
Fumaric acid	Fumarate	4.166	4.0	14.60	9.96	12.28
Acetic acid	Acetate	4.565	4.0	14.60	3.99	9.29
Malic acid	Malate	4.728	4.0	14.60	2.73	8.67
Acetic acid	Acetate	4.655	5.0	14.60	39.76	27.18
Malic acid	Malate	4.728	5.0	14.60	27.32	20.96
Succinic acid	Succinate	5.307	5.0	14.60	7.20	10.90
Malonic acid	Malonate	5.320	5.0	14.60	6.99	10.79
Maleic acid	Maleate	5.842	5.0	14.60	2.10	8.35
Succinic acid	Succinate	5.307	6.0	14.60	72.00	43.30
Malonic acid	Malonate	5.320	6.0	14.60	69.88	42.24
Maleic acid	Maleate	5.842	6.0	14.60	21.01	17.80

The pK values are measured values at 37° C. and an ionic strength of 160 mmole/l.

Results:

1. As a function of the pH-setting of the acid solution, which takes place for galenic reasons, only a limited number of organic acids can be used.

2. If the base concentration of the organic acid (metabolizable anion) is to be in a therapeutic range between approximately 10 and 50 mmole/l, based on the finished solution, only a limited pH-range can be used for the acid single solution.

TABLE II

Combination solution, pH 5.0
Example for the composition of the acid solution and the base concentrations in the finished solution, if several metabolizable organic acids or their bases (anions) are to be combined (details based on 37° C., concentration (c) in mmole/l)

			Acid Single Solution			Finished Solution
Acid	Base	pK	pH	cAcid	cBase	cBase
Fumaric acid	Fumarate	4.166	5.0	4.867	33.21	19.04
Succinic acid	Succinate	5.307	5.0	4.867	2.40	3.63
Maleic acid	Maleate	5.842	5.0	4.857	0.70	2.78
	Sum		5.0	14.60	36.31	25.45

TABLE III

Single solutions with malonic acid/malonate, pH = 4.0 to 6.0
Examples for the composition of the acid single solution and the base concentrations in the finished solution, if the same metabolizable acid or its base (anion) is to be used at different pH-values (details based on 37° C., concentration (c) in mmole/l)

			Acid Single Solution			Finished Solution
Acid	Base	pK	pH	cAcid	cBase	cBase
Malonic acid	Malonate	5.320	4.0	14.60	0.7	7.65
Malonic acid	Malonate	5.320	5.0	14.60	6.99	10.79
Malonic acid	Malonate	5.320	6.0	14.60	69.88	42.24

Measurement results

Measurement of the pH-value (mean value of 10 measurements, 37° C.) before and after mixing the alkaline single solution (HCO_3^-/CO_3^{--}) with the acid single solution (Na^+, K^+, Ca^{++}, organic acid, organic base, Cl^-) in a ratio of 1:1 with the aim of obtaining in the finished solution pH = 7.40 ± 0.05, $cHCO_3^{31}$ = 24.0 mmole/l, cNa^+ = 140 mmole/l, cK^+ = 4.0 mmole/l, cCa^{++} = 2.5 mmole/l (as a function of the concentration of the organic acid/base, the NaCl concentration of the acid single solution must be correspondingly adjusted).

	Alkaline single solution	Acid single solution	Finished solution
Solutions according to table I with a pH of 5.0:			
Acetic acid/Acetate	9.38	5.07	7.407
Malic acid/Malate		4.93	7.395
Succinic acid/Succinate		5.06	7.393
Maleic acid/Maleate		4.92	7.409
Combination solution according to Table II:			
Fumaric acid/Fumarate Succinic acid/Succinate Maleic acid/Maleate	9.39	4.99	7.401
Solutions according to Table III:			
Malonic acid/Malonate	9.39	4.16	7.412
Malonic acid/Malonate		4.95	7.416
Malonic acid/Malonate		5.94	*7.519

*Note
As the malonic acid has a relatively high pK-value (5.32) at a pH of 7.40 it leads to a minimum buffer effect if present in high concentration (here 42.24 mmole/l): $CO_2(H_2CO_3)$ is buffered in traces, so that there was a minimum pH-value rise (pCO_2 dropped).

The invention also relates to the use of the above-described aqueous solutions, particularly as dialysis, substitution or infusion solutions.

EXAMPLE

In the following performance example (details related to 37° C.), the alkaline single solution and acid single solution were in each case adjusted to 1 liter. The alkaline single solution contained 38.2 mmole/l of sodium bicarbonate and 12.2 mmole/l of sodium carbonate and the pH-value of the solution was 9.4.

The acid single solution contained 14.6 mmole/l of acetic acid and 39.8 mmole/l of sodium acetate and had a pH-value of 5.0.

Both solutions were completely stable in storage without using special containers preventing a diffusing in or out of CO_2. Their composition remained stable over long periods.

On combining the two single solutions 2 l, of finished solution was obtained with a CO_2 partial pressure of 40 mm Hg, a pH-value of 7.40, a bicarbonate concentration of 24.0 mmole/l and an acetate concentration of 27.2 mmole/l. This solution can be used with advantage as a dialysis, substitution or infusion solution.

I claim:

1. Sterilizable aqueous solution with substantially physiological values of the pH, bicarbonate concentration and CO_2 partial pressure, as well as with metabolizable anions in the form of two separately stored single solutions, which are combined with one another prior to use and whereof one is a bicarbonate-free, acid solution that is storage stable in contact with atmospheric air and the other a bicarbonate-containing, alkaline solution that is also stable in contact with atmospheric air, characterized in that per liter of the finished solution obtained by combining the two single solutions, the acid single solution contains 7.3 mmole ± 3% of at least one metabolizable, organic acid and the alkaline single solution 19.1 mmole ± 3% of alkali bicarbonate and 6.1 mmole ± 3% of alkali carbonate.

2. Solution according to claim 1, characterized in that, per liter of the finished solution obtained by combining the two single solutions, the acid single solution contains 7.3 mmole±1% of metabolizable, organic acids and the alkaline single solution 19.1 mmole±1% of alkali bicarbonate and 6.1 mmole±1% of alkali carbonate.

3. Solution according to claim 1, characterized in that the acid single solution additionally contains at least one alkali salt of at least one metabolizable organic acid.

4. Solution according to claim 3, characterized in that it contains sodium salts of metabolizable, organic acids.

5. Solution according to any one of the claim 1, characterized in that it contains as the alkali bicarbonate sodium bicarbonate and as the alkali carbonate sodium carbonate.

6. Solution according to claim 1, characterized in that the acid single solution additionally contains calcium and/or magnesium ions.

7. Solution according to claim 1, characterized in that it contains as metabolizable, organic acids pyruvic, lactic, oxalic, fumaric, acetic, succinic, malic, maleic and/or malonic acid.

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United States Patent [19]

Veech

[11] Patent Number: 4,663,166

[45] Date of Patent: May 5, 1987

[54] ELECTROLYTE SOLUTIONS AND IN VIVO USE THEREOF

[76] Inventor: Richard L. Veech, 712 Brent Rd., Rockville, Md. 20850

[21] Appl. No.: 748,232

[22] Filed: Jun. 24, 1985

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 623,510, June 22, 1984, abandoned.

[51] Int. Cl.[4] A61K 31/19; A61K 31/70; A61K 33/14; A61K 33/25

[52] U.S. Cl. 424/146; 424/153; 514/23; 514/557

[58] Field of Search 424/153, 180, 146; 514/23, 557

[56] References Cited

U.S. PATENT DOCUMENTS

3,970,750	6/1976	Brockemeyer et al.	424/153
3,993,750	11/1976	Fox	424/153

FOREIGN PATENT DOCUMENTS

WO86/239	1/1986	PCT Int'l Appl. .
WO86/227	1/1986	PCT Int'l Appl. .
WO86/228	1/1986	PCT Int'l Appl. .
WO86/335	1/1986	PCT Int'l Appl. .

OTHER PUBLICATIONS

Physicians' Desk Reference, 28th Ed. (1974), p. 125.

Latta, T., (1832), Malignant Cholera. Documents . . . Relative to the Treatment of Cholera by Copious Injection of Aqueous & Saline Fluids into the Veins, *Lancet ii;* 272–277.

Ringer, S., (1883), A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart, *J. Physiol* 4: 29–42.

Hartman, A. F., (1934), Theory & Practice of Parenteral Fluid Administration, *JAMA* 103: 1349–1354.

Locke, F. S., (1900), Die Wirkung der Metalle des Blutplasma & Verschiedener Zucker auf das Isolirte Saugerthierherz, *Zentrablatt fuer Physiologie* 14: 670–673.

Tyrode M.N., (1910), The Mode of Action of Some Purgative Salts, *Arch. Int. Pharmacedyn. 20: 205–223.*

Krebs H. A., Henseleit, K., (1932), Untersuchugen uber die Harnstoffbildung im Tierkorper, *Hoppe-Seyler's Z Physiol. Chem.* 210: 33–66.

Krebs, H. A., (1950), Body Size & Tissue Respiration, *Biochem. Biophys. Acta* 4: 249–269.

Dawson, A. M. C., Elliott, D., Elliott, W. H., Jone, K. M., (1969), Data for Biochemical Research 2nd Ed. Clarendon Press, Oxford, pp. 507, "Physiological Media".

Fox, Ch, Winfield, J. M., Slobody, L. B., Swindler C. M., Lattimer, J. K., (1952), Electrolyte Solution Approximating Plasma Concentrations with Increased Potassium for Routine Fluid & Electrolyte Replacement. *JAMA* 148: 827–833.

Mion, C. M., Hegstrom, R. M., Boen St, Scribner B. H., (1964), Substitution of Sodium Acetate for Sodium Bicarbonate in the Bath for Hemodialysis, *Trans. Amer. Soc. Artif. Int. Organs* 10: 110–113.

Parsons, F. M., Stewart, W. K., (1983), The Composition of Dialysis Fluid, In: Replacement of Renal Function by Dialysis , 2nd Ed. (Drukker, W., Parsons, F. M., Maher, J. F. eds), Martinus Nijhoff, Higham, pp. 148–170.

Facts and Comparisons, Oct. 1981–Aug. 1983. J. B. Lippincott; St. Louis 35d–53.

Documenta Geigy Scientific Tables (1962, Essellier, A. F., Jeanneret, P., Aqueous Solutions—Parenteral Infusion Therapy, pp. 331–334, Geigy Pharmaceutical Co., Ltd., Manchester.

Veech, R. L., Eggleston, L. V., Krebs, H. A., (1969), The Redox State of Free Nicotin Amide-Adenine Dinucleotide Phosphate in the Cytoplasm of Rat Liver *Biochem. J.* 115: 609–619.

Veech, R. L., Lawson, J. W. R., Cornell, N. W., Krebs, H. S., (1979), Cytosolic Phosphorylation Potential *J. Biol. Chem.* 254: 6538–6547.

Veech, R. L., Cook, G. A., King, M. T., (1980), Relationship of Free Cytoplasmic Pyrophosphate to Liver Glucose Content & Total Pyrophosphate to Cytoplasmic Phosphorylation Potential, FEBS Lett. 117: K65–K72.

Sistare, F. D., Haynes, R. C., Jr., (1985), The Interaction Between the Cytosolic Pyridine Mucleotide Redox Potential & Gluconeogenisis from Lactate/Pyruvate in Isolated Rat Hepatocytes, *J. Biol. Chem.* 260: 12748–12753.

Sistare, F. D., Haynes, R. C., Jr. (1985), Acute Stimulation by Gluconeogenisis from Lactate/Pyruvate in Isolated Hepatocytes from Normal and Adrenolectonized Rats, *J. Biol. Chem.* 260: 1254–12760.

Veech, R. L., (1986), The Toxic Impact of Parenteral Fluid Therapy, *J. Clin. Nutr.* (In Press).

Tauford, C. S., (1950), *J. Am. Chem. Soc.* 72: 441–451, Preparation & Properties of Serum Plasma Proteins, XXIII, Hydrogen Ion Equilibria in Nature & Modified Human Serum Albumin.

Primary Examiner—Stanley J. Friedman

[57] ABSTRACT

Electrolyte solutions are provided which are useful in electrolyte and fluid therapy, parenteral nutrition, and dialysis. The Na:Cl ratio is normalized, plasma and cellular pH are normalized, and cellular cofactor ratios are normalized, in a manner which decreases toxicity over prior art solutions. The solutions employ at least one of the following near-equilibrium couples: (a) bicarbonate/CO_2; (b) l-lactate/pyruvate; and (c) d-betahydroxybutyrate/acetoacetate.

15 Claims, No Drawings

ELECTROLYTE SOLUTIONS AND IN VIVO USE THEREOF

RELATED APPLICATION

This application is a continuation-in-part of U.S. Ser. No. 623,102 filed June 22, 1984, now abandoned.

BACKGROUND OF INVENTION

1. Field of the Invention

This invention lies in the field of in vivo techniques and compositions for replenishing fluid electrolytes and nutrients while regulating metabolic processes in living mammals.

2. State of the Art

The vital functions of highly developed organisms are closely dependent on the internal aqueous medium and on the maintenance in it of extreme constancy of chemical and physical properties.

It has long been recognized that all animal intracellular and extracellular body fluids contain inorganic electrolytes, and that these electrolytes are involved in, and profoundly influence, various life processes. Attempts to make artificial electrolyte fluids which may bathe tissues or be administered to the human blood stream have been known since about 1880, and, although modern analytical tools and procedures have clarified compositional details of blood electrolytes, the use of various aqueous electrolyte solutions for in vivo purposes in human medicine and related fields has been extent for approximately one hundred years.

Those inorganic electrolytes characteristically found in normal human blood serum at respective concentration levels above about 1 millimolar per liter of concentration are shown below in Table I. Also, for comparative purposes, in Table I are shown some representative compositions of various aqueous electrolyte solutions that have been previously prepared and used for in vivo purposes. In general, the philosophy behind the formulation of aqueous electrolyte solutions for in vivo use has been that such should mimic or closely resemble the chemical composition of electrolytes in blood and plasma. An electrolyte is a substance (usually a salt, acid or base) which in solution dissociates wholly or partly into electrically charged particles known as ions (the term is also sometimes used in the art to denote the solution itself, which has a high electrical conductivity than the pure solvent, e.g. water). The positively charged ions are termed cations while the negatively charged ions are termed anions. Strong and weak electrolytes are recognized. The dissociation of electrolytes is very markedly dependent on concentration; it increases with increasing dilution of the solution. The ions can be regarded as molecules in electrolyte solutions. Because of dissociation considerations, the term "sigma" or the greek letter for sigma ("Σ") is sometimes employed herein as a prefix to designate the total presence of a specified material, such as an electrolyte, whether or not all of the material is in an ionic form complexed with a heavy metal, or regardless of charge on the material in a given solution. A pair of brackets ([]) indicates the free concentration of the substance indicated as opposed to that bound to tissue components, such as proteins.

TABLE I

		Prior Art											
			Class 1a			Class 1b	Class 1c						
Units mmoles / L fluid	Normal Plasma N.E.J.M. 283, 1285 / 1970	1. a. 1 Normal 0.9% Saline U.S.	1. a. 2 Normal 0.95% Saline U.K.	1. a. 3 Isotonic Na Lactate, Salt	1. b. 1 Isotonic $NaHCO_3^-$, Salt	1. c. 1 5% Dextrose in H_2O. U.S.	1. c. 2 5.25% Dextrose in H_2O. U.K.	1. c. 3 Isotonic Glucose 2 + NaCl 1	1. c. 4 Glucose + Na Lactate + NaCl	1. c. 10 D-5-W 0.9% NaCl	1. c. 11 10% Glucose + 0.9% NaCl	1. c. 12 2.5% Glucose 0.45% NaCl	1. c. 13 5% Fructose in Electro-lyte 75
Na	136–145	155	162.5	160.3	160.3			54.1	53.4	154	154	77	40
K	3.5–5.0												35
Ca	2.1–2.6												
free $[Ca^{2+}]$	[1.06]												
Mg	0.75–1.25												
free $[Mg^{2+}]$	[0.53]												
Σ mEq Cations	142.7–153.2	155	162.5	160.3	160.3	0	0	54.1	53.4	154	154	77	75
Cl	100–106	155	162.5	108.3	108.3			54.1	36.1	154	154	77	47.5
HCO_3	26–28				52								
Σ Pi	1–1.45												
SO_4	0.32–0.94												$7.5H_2PO_4^-$
L-lactate	0.6–1.8			52.0 (d,l)					17.3 (d,l)				
pyruvate													20 (d,l)
Lact/pyr				oo					oo				oo
D B OHbutyrate													
acetoacetate													
B HB/acac													
acetate													
Other													
Σ mEq anions	128.7–139.4	155	162.5	160.3	160.3	0	0	54.1	53.4	154	154	77	75
Na/Cl	1.28–1.45	1.00	1.00	1.48	1.48			1.00	1.48	1.00	1.00	1.00	0.84
Glucose or others	3.9–5.6					278	292	195	195	278	556	139	278 (Fructose)
CO_2	0.99–1.39												
pH	7.35–7.45	5.5–6.5	5.5–6.5	~6.5	8.6	~6.5	~6.5	~6.5	~6.5	~5.5–6.5	~5.5–6.5	~5.5–6.5	
Σ mOsa	285–295	310	325	321	321	278	292	301	302	564	813	293	428
Use:													

		Prior Art											
			Class 2a										
Units mmole / L fluid	Normal Plasma N.E.J.M. 283, 1285 / 1970	Class 1d	2. a. 1. Ringer's Injection U.S.	2. a. 2. Lactated Ringer's	2. a. 3 Lactated Ringer's (Commercial)	2. a. 4. Acetated Ringer's U.S.	2. a. 5 Lact/Acet Ringer's	2. a. 10 Ionosol D-CM (Abbott)	2. a. 11. Plasmalyte (Travenol)	2. a. 12. Isolyte S (McGaw) Polyionic 148 (Cutter)	2. a. 13. Isolyte E (McGaw)	2. a. 14. Delbecco's Phosphate Saline	2. a. 15. Kreb's Ringer Phosphate	2. b. 1. Krebs Henseleit
Na	136–14		147	129.8	130	130	140	138	140	140	140	152.2	150.76	143
K	3.5–5.0		4	5.4	4	4	10	12	10	5	10	4.17	5.92	5.9
Ca	2.1–2.6		2.5	0.9	1.5	1.5	2.5	2.5	2.5		2.5	0.9	2.54	2.5
free $[Ca^{2+}]$	[1.06]													
Mg	0.75–1.25			1.0			1.5	1.5	1.5	1.5	1.5	0.49	1.18	1.2
free $[Mg^{2+}]$	[0.53]													
Σ mEq Cations	142.7–153.2		156	139	137	137	158	158	158	148	2.158	159.15	164.12	156.3
Cl	100–106		156	111.8	109	109	103	108	103	98	103	140	131.51	127.8
HCO_3	26–28													25

TABLE I-continued

Σ Pi	1–1.45												
SO_4	0.32–0.94												
L-lactate	0.6–1.8		27.8 (d,l)	28 (d,l)		27.5 (d,l)	50 (d,l)	8 (d,l)			9.83	17.38	1.18
pyruvate											0.48	2.36	1.18
Lact/pyr			oo	oo		oo	oo	oo					
D B OHbutyrate													
acetoacetate													
B HB/acac													
acetate					28	27.5		47	27	49			
Other									23 (gluconate)	4 citrate			
Σ mEq anions	128.7–139.4	156	139	137	137	158	158	158	148	158	159.18	165.15	157.3
Na/Cl	1.28–1.45	0.94	1.16	1.19	1.19	1.36	1.28	1.36	1.43	1.40	1.08	1.15	1.12
Glucose	3.9–5.6												
or others													
CO_2	0.99–1.39												
pH	7.35–7.45												1.24
Σ mOsa	285–295	309	276	272	272	312	312	312	294	315	7.4	7.4	7.4
Use:		I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	I.V. electrolyte therapy	I.V. electrolyte therapy	I.V. electrolyte therapy	I.V. electrolyte therapy	308 Usually tissue culture, sometimes cardiac surgery	311.16 Biochemical experiments	308 Multiple Biochemical Uses

		Prior Art										
		Class 2c							Class 2d			
Units	Normal Plasma N.E.J.M. 283, 1285	2. c. 1 Lactated Ringer's +	2. c. 2 ½ Strength Lact-Ringer +	2. c. 3. Acetated Ringer's +	2. c. 4. Ionosol B +	2. c. 5. Dianeal +	2. c. 6. Peritoneal Dialysis +	2. c. 7. Dianeal K14 +	2. d. 1 Krebs Serum	2. d. 2 Tyrode's Solution I	2. d. 3. Tyrode's	2. d. 4. Locke's
mmoles												
L fluid	1970	5% Glucose	2.5% Glucose	Glucose	5% Glucose (Abbott)	1.5% Glucose (Travenol)	4.25% Glucose (Am. McGaw)	4.25% Glucose (Travenol)	Substitute	(Schimassek)	Solution	Solution
Na	136–145	130	65	130	57	141	141.5	132	141	151.54	150.1	157.57
K	3.5–5.0	4	2	4	25			4	5.93	5.9	5.9	3.57
Ca	2.1–2.6	1.5	0.75	1.5		1.75	2.0	1.875	2.54	1.8	1.8	2.16
free $[Ca^{2+}]$	[1.06]											
Mg	0.75–1.25				2.5	0.75	0.75	0.75	1.18	0.45	0.45	0
free $[Mg^{2+}]$	[0.53]											
Σ mEq Cations	142.7–153.2	137	68.5	137	87	146	147	141	154.37	162.07	160.5	165.46
Cl	100–106	109	55	109	49	101	102.5	106	104.8	147.48	147.48	163.92
HCO_3	26–28								24.9	11.9	11.9	3.57
Σ Pi	1–1.45				6.5 $H_2PO_4^-$				1.23	1.22	1.22	—
SO_4	0.32–0.94								2.36			
L-lactate	0.6–1.8	28 (d,l)	14 (d,l)		25 (d,l)	45 (dl)		35 (d,l)		1.33		
pyruvate									4.9	0.09		
Lact/pyr		oo	oo		oo	oo		oo		14.8		
D B OHbutyrate												
acetoacetate												
B HB/acac												
acetate				28			44.5					
Other									2.45 glutamate$^-$ 5.4 fumarate^{2-}			

TABLE I-continued

Σ mEq anions	128.7–139.4	137	69	137	87	146	147	141	154.47	162.81	161.6	167.49
Na/Cl	1.28–1.45	1.19	1.18	1.19	1.16	1.40	1.38	1.25	1.35	1.03	1.02	0.96
Glucose or others	3.9–5.6	278	139	278	278	83	236	236	9.2	5.45	5.6	5.6–13.7
CO_2	0.99–1.39								1.0	1.17		
pH	7.35–7.45					~5.5–6.5	~5.5–6.5	~5.5–6.5	7.4	7.1	7.1	?
Σ mOsa	285–295	524	263	523	443	366	510	494	308.2	328	318.3	336
Use:		I.V. fluid nutrition & electrolytes	I.V. fluid for de-hydration	same as 2. c. 1.	Parenteral Nutrition	Peritoneal Dialysis	Peritoneal Dialysis	Peritoneal Dialysis	Artificial Serum for Tissue Slices Normal Na/Cl	Liver Perfusion		

Class 1a Solutions Containing 1 or 2 Cations, no Nutrients and No HCO_3^-/CO_2

1. a. 1. Most common U.S. I.V. electrolyte solution, Merck Manual. Causes hyperchloremic acidosis with Na/Cl = 1.00. See Black DAK. Lancet i, 353, 1952.
1. a. 2. Used as "normal" saline in U.K. and Canada. Geigy Handbook.
1. a. 3. Darrow et al. J. Am. Med. Ass. 143: 365, 432, 1944. Normal Na/Cl ratio but causes abnormalities.

Class 1b. Solutions Containing 1 or 2 Cations, HCO_3^-, and No Nutrients.

1. b. 1. Darrow et al. J. Am. Med. Ass. 143: 365, 432, 1944. Use of bicarbonate alone to correct Na/Cl ratio gives a solution with an abnormal pH, and one which will cause Ca^{2+} or Mg^{2+} added to the solution to precipitate as $MgCO_3$ or $CaCO_3$, is the common alternative to Na lactate, salt; 1. a. 3.

Class 1c Solutions Containing 1 or 2 Cations, with Non-ionic Nutrients. Typically 2.5%, 5%, 10%, 20%, Glucose or Fructose in the U.S. and 2.62%, 5.25%, 10.5%, 20% Glucose or Fructose in the U.K.

1. c. 1. Most used I.V. solution in the U.S. Merck Handbook, 1966, p. 1867. This is combined with NaCl in varying proportions so long as the osmolarity is not below 270 mOsa.
1. c. 2. Same solution in the U.K., where "isotonic" differs. Geigy Handbook, 1970, p. 334.
1. c. 3. Geigy Handbook, 1970, p. 334, has Na/Cl = 1.00
1. c. 4. Geigy Handbook, 1970, p. 334, has reasonable Na/Cl ratio but induces an abnormal redox state.
1. c. 10. throught 1. c. 12. See Facts and Comparisons p. 51, Oct. '81, Lippincott
1. c. 13. Facts and Comparisons p. 52, Aug. '83, Lippincott. Used in parenteral nutrition.

Class 1d Solutions Containing 1 or 2 Cations, Nutrients, and HCO_3^-/CO_2. None in prior art.

Class 2a Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contacting Cells, Containing No HCO_3^-/CO_2 and No Glucose; eg. after S. J. Ringer, Physiol 4: 29, 223, 1883.

2. a. 1. Facts and Comparisons p 50, Oct '81, Lippincott
2. a. 2. Hartmann AF. J. Am. Med. Ass. 103: 1349, 1934.
2. a. 3. Facts and Comparisons p 50, Oct '81, Lippincott.
2. a. 4. Facts and Comparisons p 50, Oct '81, Lippincott.
2. a. 5. Fox et al. J. Am. Med. Ass. 148: 827, 1952.
2. a. 10. Facts and Comparisons p 50, Oct '81, Lippincott.
2. a. 11. Facts and Comparisons p 50, Oct '81, Lippincott.
2. a. 12. Facts and Comparisons p 50, Oct '81, Lippincott.
2. a. 14. Delbecco R, Vogt M. J Exp Med 1954; 99: 167–182
2. a. 13. Facts and Comparisons Oct, 1981, p. 50, Lippincott, St. Louis
2. a. 15. Krebs HA. Hoppe S 2 Physiol Chem 1953; 217: 193

Class 2b Solutions Containing 3 or 4 Cations, HCO_3^-/CO_2 and No Glucose or Other Non-Ionic Nutrients.

2. b. 1. Krebs HA, Henseleit K. Hoppe-Seyle's 2 Physiol Chem 1932; 210: 33–66. This is the second major advance in fluids after S. J. Ringer, Physiol 1883; 4: 29, 223. This fluid became the basis for most tissue culture "balanced salt mixtures", was used in dialysis. It is known to contain twice too much Ca and Mg. It also has an abnormal Na/Cl ratio which Krebs himself unsuccessfully attempted to correct in 1950. (See Krebs HA. B B A 1950;
4: 249–269, or Table I class 2d.)

Class 2c Solutions Containing 3 or 4 Cations, No HCO_3^-/CO_2 to Which is Added Non-Ionic Nutrients.

2. c. 1. Multiple Manufacterer's. Facts and Comparisons p. 52, Oct 81
2. c. 2. Multiple Manufacterer's Facts and Comparisons p 52. Oct 81
2. c. 3. Multiple Manufacterer's Facts and Comparisons p 52, Oct 81
2. c. 4. (Abbott) Facts and Comparisons p 52b, Aug '83
2. c. 5. (Travenol) Facts and Comparisons p 704, Oct '82
2. c. 6. (American McGaw) Facts and Comparisons p 704, Oct '82

TABLE I-continued

2. c. 7. (Travenol) Facts and Comparisons p 704, Oct '82

Class 2d Solutions Containing 3 or 4 Cations, Plus Non-Ionic Nutrients and HCO_3^-/CO_2

2. d. 1. Krebs HA, B.B.A. 4: 249-269, 1950. Not used in vivo but presented for comparison of composition.

2. d. 2. Tyrodes's solution as modified for liver perfusion by Schimassek H, Biochem Z 336: 460, 1963. Not used in vivo but presented to show prior art in composition. Same for 2. d. 3, Tyrode's, and 2. d. 4, Locke's.

2. d. 3. Tryrode MV, Arch Int Pharmacodya Ther 20: 205-223, 1910.

2. d. 4. Locke FS, Zeatbl Physiol 14: 670-672, 1900.

Contemporarily, a large number of different aqueous electrolyte solutions are prepared, sold in commerce, and used as in vivo fluids, such as for electrolyte and fluid replacement, parenteral nutrition, and dialysis (both hemo-and peritoneal).

Even a cursory examination of Table I will confirm the medical dicta that "plasma is an unmakable solution". The solutions listed in Table I illustrate this belief. The essential problem is that plasma contains, in addition to major inorganic electrolytes, trace quantities of various electrolytes plus various metabolites including plasma proteins. In practice, it has not been possible to construct synthetically a replication of plasma because of it complexity. Blood, extracellular fluid, and even plasma can be regarded as tissues.

In most prior art electrolyte solutions, the concentration of chloride anions (Cl^-) is higher than in human plasma or serum. For example, the Krebs Henseleit solution (see Table I) contains a concentration of Cl^- which is about 20% higher than in human serum. This anion gap, that is, the difference between the positive cations and the negative anions, is now known to be due largely to the anionic metabolites in normal plasma plus the contribution of acidic amino acid groups found on plasma proteins. Referring to Table I, it is seen that the total positive cations in plasma is 142–154 meq/l while the total anions is only about 128–137 meq/l leaving a deficit of about 14–17 meq/l of anions. For convenience, the anion gap in human plasma can be expressed as the ratio of sodium cation milliequivalents per liter to chloride anion milliequivalents per liter.

From Table I, it is clear that the Krebs Serum substitute (Krebs, H. A. *Biochem. Biophys. Acta* 4, 249–269, 1950) comes closest to approximating the electrolyte composition of human plasma. In this solution, Krebs attempted to correct the excessive Cl^- content in Krebs Henseleit solution (*Hoppe-S Z. Physiol. Chem.* 210, 33-66, 1932) using metabolic experiments with tissue slices. Because of the law of electrical neutrality, Na^+ cannot be added to a solution without some anion (such as Cl^-) being added also; the sum of cations and anions must be equal in any solution. In his 1950 attempt, Krebs chose pyruvate$^-$, l−-glutamate$^-$, and fumarate^{2-} as anions to be added.

An alternative to Krebs selection of anions came about at the same time. In 1949, the use of high concentrations of acetate as a metabolizable organic anion was advocated (Mudge G. H. Mannining, J. A. Gilman A.; *Proc. Soc. Exptl. Biol. Med.* 71, 136–138, 1949). This idea led in 1964 to the advocacy of the use of 35–45 mM (millimolar) acetate in commercial hemodialysis fluids (Mion C. M., Hegstrom R. M., Boen S. T., Scribner B. H.; *Trans. Am. Soc. Artif. Internal Organs* 10, 110–113, 1964).

In addition to the above organic anions, the current reference work "Facts and Comparisons" indicates various commercial electrolyte fluids which contain lactate anion.

All of the prior art electrolyte solutions (with or without nutrients) as exemplified in Table I are now believed to lead to undesirable and pathological consequences particularly through extended usage. As regards acetate, editorials recently appearing in the *British Medical Journal*, 287, 308–309, 1983) present evidence that acetate leads to fatigue, nausea, malaise, sudden hypertension, increased atherosclerosis, hypoventilation, and hypoxia. Also, the originator of acetate dialysis now advocates its use only in "healthy" patients (Pagel M. D., Ahmed S, Vizzo J. E. and Scribner B. H.; *Kidney Int.* 21, 513–518, 1982).

Krebs choice of glutamate$^-$ and fumarate^{2-} is incorrect because these anions do not penetrate cell membranes in a predictable manner, but, like citrate^{3-}, exhibit severe gradients of six fold or greater between plasma H_2O and cell H_2O. The alternate use of d,l-lactate$^-$ (Hartmann AF. *J Am Med Asso* 103 1349–1354, 1934) is now known to induce severe abnormalities, particularly coma at levels far below the 28 to 35 mM d,l-lactate contained in these solutions (Oh MS et al, *N Eng J Med* 301 249 251, 1979; Stolberg L, et al *N Eng J Med* 306: 1344–1348, 1982; Ballabriga A, et al *Helv Paediatr Acta* 25:25–34, 1970) in to the induction severe abnormalities in redox and phosphorylation state induced by the use of l-lactate alone. The use of gluconate$^-$ induces abnormalities in the hexosemonophosphate pathway. Indeed, all previous used organic ions violate the "safe entry points" or the normal Na:Cl ratio as herein defined.

In addition to the use of d,l-lactate, gluconate, fumarate, glutamate, pyruvate, and citrate anions in current commercially available prior art electrolyte fluids, and wherein such anions are typically employed at levels above those found in the (plasma or serum) of healthy humans, many such prior art commercial fluids also employ high levels of nonionic metabolites, such as fructose and glycerol, which induce separate redox state and phosphorylation potential abnormalities in phosphorylation potential with rapid destruction of liver purine nucleotides and their release into blood sometimes leading to renal shutdown due to uric acid deposition in the kidneys (see Woods H. F., Eggleston L. V. and Krebs H. A.; *Biochem. J.* 119, 501–510, 1970). Fructose in plasma above 0.2 mM must be considered to violate the "safe entry point". Likewise, use of intravenous glycerol at levels above 5 mM/l as currently practiced leads, in tissue containing glycerol kinase, such as kidney and liver, to accumulation of 10 mM glycerol phosphate (over 100 times normal). See Burch H. B. et al.; *J. Biol. Chem.* 257, 3676–3679, 1982).

In addition to failing to solve the anion gap problem (or to provide a normal milliequivalent ratio of sodium cation to chloride anions) without causing profound and adverse physiological effects (including disruption of normal redox state and normal phosphorylation potential), many prior art aqueous electrolyte solutions for in vivo usage fail to have a pH which approximates the pH of mammalian intracellular and extracellular fluids, especially, plasma or serum.

Mammalian systems normally operate at temperatures between about 37°–38° C. where, by common thermodynamic convention, neutral pH is taken to be about 7 at 25 C. It is clear that changes in pH, (the negative log 10 of [H+] concentration) necessarily affect the fundamental energetic relationships occurring in living cells. Also, enzymes have sharply defined ranges of "H+] concentration in which they perform their catalytic functions in a normal manner. Deviation of mammalian plasma pH down to 6.9 or above 7.7 from its normal range of 7.35–7.45 is therefore fatal to most mammalian organisms. Massive changes in the cellular redox and phosphorylation states also disorder cellular homeostasis.

The pH of human plasma is normally maintained by the human body in the range from about 7.35 to 7.45 while the pH of human cellular cytoplasm is about 7.2 (see Veech et al in *J. Biol. Chem.* 254, 6538–6547, 1979).

If blood pH drops to 6.8 in man, then death ensues from cardiac arrest, and if blood pH increases to above pH 7.7, then death ensues from convulsions.

The major chemical system maintaining body pH within this narrow normal range is the $[CO_2]/[HCO_3^-]$ buffer system. The $[CO_2]$ of blood is maintained minute to minute by a portion of the mammalian brain called the respiratory center which senses brain cell pH and adjusts the depth and speed of respiration to change pH by increasing or decreasing $[CO_2]$ according to the famous Henderson Hasselbalch equation (Henderson L. J., *Silliman Lectures, Yale U. Press, New Haven,* 1928).

Even though pH is thus seen to be a critical factor in mammalian blood, many commercial electrolyte solutions as administered have pH values which deviate substantially from normal. Others give excessive Cl^- relative to Na^+ which results in hyperchloremic acidosis, (Black D.A.K.; *Lancet i* 305-12, 1953), or give organic anions in a manner which causes measurable deviations from normal in the metabolic processes of the cell. Also, many commercially available electrolyte solutions contain no carbon dioxide which can result in a loss of respiratory drive and consequent hypoxia in patients.

The compositions and methods of the present invention overcome the above indicated prior art problems. These compositions and methods employ definite ratios of [bicarbonate$^-$]/[carbon dioxide], [l-lactate$^-$]/[pyruvate$^-$], and [d-betahydroxybutyrate$^-$]/[acetoacetate$^-$]. Each of these mixtures constitute a near equilibrium couple which is known to be a normal constituent of mammalian plasma. While each of these pairs of components has been previously employed at lease on a laboratory basis in solutions used for animal (mammalian) experiments, these mixture pairs have never previously been used in an electrolyte solution to obtain a normal Na:Cl milliequivalent ratio or to solve the anion gap problem.

All previous electrolyte solutions, and plasma substitutes, induce severe and measurable pathogenic abnormalities and no prior art electrolyte solution or plasma substitute has both (a) employed at least one of the three mixture pairs of this invention and (b) achieved a normal Na:Cl milliequivalent ratio as taught herein. Thus, for example, the Krebs Henseleit solution contains the $[HCO_3^-]/[CO_2]$ buffer system (but contains excessive chloride ions). Schimassek (Schimassek H.; *Bio. Chem. Z,* 336, 460, 1963) added about normal blood levels of lactate and pyruvate to what is essentially Tyrode's solution (see Tyrode, M. J.; *Arch Int. Pharmacodyn* 20, 205, 1910) containing 2.5% albumin in an attempt to create a physiological solution for perfusion. It should be noted that Schimassek added 1.33 mM/L D-L-lactate, which is definitely abnormal (see normal blood lactate levels shown in Table 1). Further, the Na^+ of 151 mM/l and Cl^- of 147.5 mM/l in Schimassek's modified Tyrode's solution approximates the concentration of 155 mM/l Na and 155 mM/l Cl in so-called normal (0.9T) saline, the most widely used electrolyte infusion solution, and thus obtained a grossly abnormal Na:Cl milliequivalent ratio of about 1.24–1.45 with a mean of about 1.38. Infusions of electrolyte solutions with a Na:Cl milliequivalent ratio of less than about 1.38 have long been known to cause hyperchloremic acidosis in the treated organism. (See Levinsky N. G. in Harrison's *Textbook of Medicine* pp 230–236, McGraw-Hill, N.Y., 1983). It is the attempt to avoid this problem that leads to the wide use of such solutions as Ringer's lactate or acetate dialysis fluids which overcome the Na:Cl ratio problem, but which in turn create gross abnormalities of other types. It is the attainment of a normal Na:Cl milliequivalent ratio in a manner which avoids the pathological consequences inherent in all currently known or practiced methods which is a major part of the invention herein disclosed.

The making of a Krebs Henseleit electrolyte solution (or other prior art electrolyte solution) and the incorporation thereinto of a mixture of L-lactate and pyruvate anions, or of a mixture of D-betahydroxybutyrate and acetoacetate anions did not, and could not, result in the making of an electrolyte solution wherein the anion gap problem was overcome (or wherein the milliequivalent ratio of sodium cations to chloride anions was normalized), in accordance with the teachings of the present invention, because each of such resulting solutions would still contain excessive chloride anions and so would inevitably cause hyperchloremia if an when used in human or mammalian therapy.

In general summary, the prior art describes a series of electrolyte solutions typically of about 270–320 milliosmoles (or higher) comprised of: (a) 1 to 4 metallic cations of sodium, potassium, magnesium, and calcium in amounts greater than 0.5 mM/L, (b) 1 to 5 inorganic anions of chloride plus also HPO_4^{2-}), (c) 0 to several organic carboxylic or bicarbonate anions, (d) 0 to 5 nonionic materials in concentrations of greater than about 0.5 mM/L from the group comprising CO_2 gas, glucose, urea, glutamine, and others, and (e) sometimes one or more high molecular weight substances, such as albumin, hemocel, and the like. None of these solutions, for the reasons herein above explained, either normalize the milliequivalent ratio of Na:Cl at all, or normalize this ratio without causing profound and adverse physiological consequences. In the present invention, there are provided processes and compositions of a complex fluid nature for in vivo usage which can substantially completely eliminate all of such prior art problems. While the components of these new solution compositions are known solution components, no one has heretofore formulated the solutions of the present invention which not only tend to achieve a normal plasma milliequivalent ratio of sodium cations to chloride anions, but also tend to achieve a normalization of plasma pH and a normalization of the cellular redox state and the cellular phosphorylation potential. Also, these new solutions permit one to avoid usage of the previously employed carboxylic anions, as acetate, or lactate alone, which cause adverse effects.

BRIEF SUMMARY OF THE INVENTION

This invention relates to processes for accomplishing electrolyte and water therapy while simultaneously normalizing blood composition in a mammal (including man) by introducing in a physiologically effective amount by any means, including parenterally, (intravenously), intra-arterially, intramuscularly, intravascularly, and the like, by dialysis, or orally, and the like into such mammal an aqueous solution wherein:

(a) the ratio of sodium cation milliequivalents per liter to the chloride anion milliequivalents per liter are so selected as to tend to produce the range found in normal mammalian blood plasma,

(b) there is a physiologically effective amount of at least one near equilibrium couple selected from the group consisting of

(1) bicarbonate$^-$ and carbon dioxide,

(2) l-lactate$^-$ and pyruvate$^-$, and

(3) d-betahydroxybutyrate$^-$ and acetoacetate$^-$, and

(c) the pH ranges from 5 to 9.

This invention further relates to physiologically compatible aqueous salt solutions for mammalian (including human) administration which contain such a ratio of sodium to chloride and which incorporate such near-equilibrium couples(s).

This invention provides electrolytes of the class indicated wherein physiologically normal concentrations of the divalent cations Mg^{2+} and Ca^{2+} may be included without precipitation. No one has previously made solutions for in vivo use which contain the correct Na^+:Cl^- ratio and which also contain the physiologically normal respective amounts of Mg^{2+} and Ca^{2+}.

When used for mammalian administration in accord with the present process teachings, such a solution:

(a) tends to maintain and normalize in plasma the milliequivalent ratio of sodium cations to chloride anions in the normal range, and

(b) tends to maintain and normalize plasma pH, and

(c) tends to maintain and normalize the redox state and the phosphorylation potential.

One (first) class of such solutions chracteristically utilizes (contains) an inorganic class of anions comprised of chloride and bicarbonate. These solutions have a physiological pH which is broadly in the range from about 5 to 9, and preferably in the range from about 6.9 to 8.6, and more preferably in the range from about 7.35 to 7.45, and most preferably is about 7.4 (for human use). Dissolved carbon dioxide is also present in these solutions. When administered, these solutions not only tend to maintain the treated mammal's normal blood (and plasma) ratio of sodium to chloride, but also tend to set (regulate) the treated mammal's blood (plasma) pH at a normalized value. In addition the treated mammal's redox state and phosphorylation potential tend to be normalized.

Another (second) class (preferred) of such solutions characteristically utilizes (contains) chloride anions and a class of carboxylate anionic mixture couples comprised of at least one member from the group consisting of (a) a mixture of l-lactate$^-$ anions and pyruvate$^-$ anions, (b) a mixture of d-betahydroxybutyrate$^-$ anions and acetoacetate$^-$ anions, and (c) a mixture of both (a) and (b). These solutions have a physiological pH which is as above defined in connection with such (first) class of solutions. When administered, these solutions not only tend to maintain the treated mammal's redox state within a normal range, but also tend to maintain that mammal's phosphorylation potential within a normal range.

Another (third) class (more preferred) of such solutions characteristically utilizes (contains) both chloride anions, and bicarbonate/carbon dioxide mixture, as in such (first) class of solutions, but also utilizes (contains) such class of carboxylate anionic couples, as in such (second) class of solutions. When administered, these solutions achieve the above indicated effects obtained from the use of such (first) class of solutions and the above indicated effects obtained from the use of such (second) class of solutions.

The specified milliequivalent ratio of sodium to chloride in normal mammalian blood generally is believed to be in the range from about 1.24:1 to 1.47:1. In the case of a normal human adult, this range is now believed to extend (based on published information) from about 1.24:1 to 1.45:1 and preferably from about 1.33:1 to 1.42:1 and most preferably from about 1.36:1 to 1.42:1. These ratios of Na^+:Cl^- are typically employed in solutions used in the practices of this invention. Ratios above 1.47, i.e. from about 1.47 to about 1.6 can be used within the spirit and scope of this invention as when it is the physician's conscience intention to create an abnormal Na^+:Cl^- ratio as, for example, to create an excess of alkali reserve; however, such higher ratios are generally not presently preferred for general usage. In the case of dialysis fluids or to create an alkalotic condition in a cell or to correct an existent acidosis, this Na^+:Cl^- ratio could range from a normal value (about 1.24 to 1.45) to about 1.6.

In using these couples, the important factor is the ratio of the concentration of [product]/[reactant] (see Eqns 0,1,2,3,4,5 & 7 hereinbelow). The absolute concentration becomes important in affecting the chemical activity of water (e.g. the osmotic pressure).

The total quantity, or sum (sigma), of each of the couples (bicarbonate/CO_2, l-lactate/pyruvate, and d-betahydroxybutyrate/acetoacetate) present in a solution of this invention can range from 0 to about 465 mMoles/liter of solution. However, in routine situations, the quantity of each couple commonly ranges from 0 to about 25 to 60 mMoles/liter.

Preferably, the ratio of bicarbonate milliequivalents per liter to dissolved carbon dioxide milliequivalents per liter in a solution of this invention can range from about 0.1:1 to 55:0.1 and preferably 11:1 to 24:1. More preferably, such total ranges from about 10 to 45 mM/l and such ratio ranges from about 18:1 to 26:1, and still more preferably such total ranges from about 23 to 35 mM/l while such ratio ranges from about 19:1 to 21:1. A ratio of 19.95 for $[HCO_3^-]/[CO_2]$ gives a pH 7.4, which is presently particularly preferred.

Preferably, the ratio of l-lactate anion milliequivalents per liter to pyruvate anion milliequivalents per liter in a solution of this invention can range from about 20:1 to 1:1. Preferably, such total quantity ranges from about 0.5 to 10 mM/l and such ratio ranges from about 3:1 to 15:1, and more preferably such total quantity ranges from about 2 to 8 mM/l while such ratio ranges from about 5:1 to 12:1.

Preferably, the ratio of d-betahydroxybutyrate anion milliequivalents per liter to acetoacetate milliequivalents per liter in a solution of this invention can range from about 6:1 to 0.5:1. Preferably, such total ranges from about 1 to 10 mM/l and such ratio ranges from about 4:1 to 1:1, and more preferably such total ranges from about 2 to 5 mM/l while such ratio ranges from about 3:1 to 1.5:1.

By the term "milliequivalent ratio" as sometimes used herein, reference is had the ratio of milliequivalents per liter of one substance to milliequivalents per liter of another substance in an aqueous medium.

One of the three near equilibrium couples employed in the practice of this invention (the bicarbonate$^-$/carbon dioxide couple) tends, as used in this invention, to regulate the concentration of hydrogen ions in blood (plasma) and in the treated mammal's cells, and each one of such couples tends to normalize the redox state of each of the three pyridine nucleotide couples. The phosphorylation potential also tends to be normalized. Also, each such near equilibrium couple when used as herein described constitutes a safe entry point into the metabolic system of a mammal.

By the term "safe entry point" as used herein reference is generally had to a metabolite which, in living tissue or cells:

(1) does not cause a massive buildup of one or more of intermediate cellular metabolites,

(2) does not cause a severe disruption of any one of the controlling nucleotide ratios in a living cell,

(3) can be added to a physiological system of a living mammal at a concentration level which is greater than that which is found normally in such system (such as blood plasma of a fasting mammal) without causing any appreciable distortion in metabolism and without causing any pathological conditions to arise, and

(4) may be found in normal variants of the physiological state as when the total of d-betahydroxybutyrate plus acetoacetate reaches a level of about 8 to 10 mM/l in three-day fasting man, or the total of l-lactate plus pyruvate rises to a level of about 5 to 6 mM/l in a jogging normal man.

Further, each such above described near equilibrium couple in this invention exhibits a distribution or permeability between intracellular fluid and extracellular fluid such that the ratio of the concentrations in, respectively, intracellular fluid to extracellular fluid ranges from about 1.0:1 to 1.5:1 in most all mammalian cells.

These respective three pairs of permeant monocarboxylate near equilibrium couples are unique among metabolites in being osmotically neutral in respect to the water in intracellular and extracellular space. Administration of these three couples, as their appropriate cationic salts (individually or in some combination with one another as taught herein) necessarily results in no net change in the distribution of water between intracellular and extracellular spaces in most tissues. By administration of varying ratios of these couples, however, the physician may control the distribution of water by varying the redox state and hence the phosphorylation state as described in equation 7 herein below. Osmotically active substances incorporated with the solutions of this invention preferably should each constitute a safe entry point. For example, glucose above 13 mM/l is higher than ever occurs under normal physiological conditions in a healthy man. Use of glucose above 13 mM/l (as in the widely used 5% glucose solution) as a calorie source is, apart from consideration of the source of pathology, and apart from the carboxylate couples, considered herein to be an acceptable source of calories. The extreme ability of the mammalian body to regulate its glucose metabolism makes it far to be preferred over other possibly nonionics, such as fructose or glycerol, which enter the metabolic system in an uncontrolled manner causing pathologic changes such as are already referenced, and so such are not safe entry points.

Characteristically, a solution used in the practice of this invention can contain from about 1 to 2400 millimoles per liter of sodium cations, but, in routine situations, commonly ranges from about 120 to 170 mM/L and more preferably from about 129 to 163.5 mM/l and most preferably from about 136 to 145 mM/l.

In addition, a solution contains sufficient chloride anions to produce a milliequivalent ratio of sodium cations to chloride anions in the range above defined.

Optionally, in addition to sodium, a solution of this invention can contain one or more of the following additional metallic cations each in a respective quantity as below indicated:

TABLE II

cation component	Quantity range (millimoles per liter) broad	preferred	more preferred
potassium	0-90	0-40	0-5
calcium	0-60	0-10	0-1.5
magnesium	0-15	0-10	0-1

Optionally a solution of this invention can have additionally incorporated (dissolved) therein from 0 to about 2400 millimoles per liter of at least one osmotically active substance which is preferably metabolizable and preferably substantially nonionic (including zwiterionic).

A solution used in the practice of this invention is further characterized by generally having:

(1) sufficient total substances dissolved therein to produce an osmolarity ranging from about 260 to 5000 milliosmoles/liter (mOs), and preferably from about 265 to 550 mOs, and more preferably from about 280 to 320 in mOs, and most preferably about 311 milliosmoles/liter.

(2) the relationship between total (dissolved) ionic substances is such that the pH ranges from about 5 to 9, and preferably from about 6.9 to 8.6; and most preferably from about 7.35 to 7.55;

(3) the charges of all cations equal the charges of all anions; and

(4) the minimum total concentration of all such near equilbrium couple(s) present is at least about 0.1 millimoles per liter, and preferably is at least about 0.5 mM/l, and more preferably about 2 mM/l, while the maximum concentration thereof is preferably not more than about 465 mM/L and more preferably is not more than about 65 mM/l and most preferably is not more than about 50 mM/l.

Examples of usable osmotically active substantially nonionic substances include glucose, glycerol, fructose, sorbitol, and the like. Glucose is presently most preferred.

As hereinbelow explained, the processes and the solutions of the present invention find use in a wide variety of therapeutic applications, such as in electrolyte and fluid replacement, parenteral nutrition, and dialysis.

Various additional objects, aims, purposes, features, advantages, applications, variations, and the like will be apparent to those skilled in the art from the teachings of the present specification taken with the claims.

DETAILED DESCRIPTION

This description is based upon best available information (including theory) known to the inventor. Any misdescription or the like, if such should exist, is not believed to alter the fundamentally correct basis and evidence supporting the present invention.

A. The Redox State

In biological cells, most reactions are catalyzed by enzymes of which an average cell may have of the order of 10^4. In ne classification, enzymes may be grouped in only six functional categories:

(1) dehydrogenases which transfer H^+ and e^- from one substrate to another by the use of cofactors, such as NAD^+ (nicotinamide adenine dinucleotide), or prosthetic groups, such as FAD (flavin adenine dinucleotide), or others;

(2) kinases or phosphotransferases which effect the group transfer of a phosphate to a substrate usually by using a co-factor, such as ATP or other similar phosphate-containing compounds;

(3) carbon-carbon bond group transferases which either or break carbon-carbon bonds using co-factors of the co-enzyme A type or occur on a solid state substrate, such as a glycogen particle, or the surface of a fatty acid synthase multi-enzyme complex;

(4) isomerases which effect internal rearrangements within a compound;

(5) hydratases which either add or subtract water from a substrate; and

(6) peptidases which break C-N bonds or create such bonds again usually taking advantage of a solid state synthetic matrix, such as a ribosome.

A special class of substrates taking part of biological reactions catalyzed by enzymes are called co-factors or co-enzymes. Co-enzymes, such as, for example, NAD, become attached and detached from an enzyme during a catalytic cycle, while prosthetic groups, such as flavin nucleotides or cytochromes, remain firmly attached during the catalytic cycle.

Since co-enzymes take part in multiple intracellular reaction within a given cellular compartment, the chemical potential of the co-enzyme couple becomes of central importance in energy transformation and oxido-reductions occurring in living matter. The thermodynamic characteristics of a particular whole set of oxido-reduction reactions is dependent upon the ratio of the free concentrations (strictly speaking, the activities) of the free [NAD+] and free [NADH]ratio. The ratio [NA(P)D+]/[NAD(P)H], thus represents and defines the redox state, at a given pH, of a particular pyridine nucleotide couple, and this ratio then determines:

(1) the extent and direction of reversible reactions in near-equilibrium with the co-enzyme couple;

(2) the extent to which a co-enzyme couple can be effective as an intracellular reducing agent, for example, in reducing the beta-oxoacyl co-enzyme A to beta-hydroxyacyl-coenzyme A; and

(3) the magnitude of the free-energy changes of oxido-reductions in the electron transport chain responsible for the major portion of ATP synthesis.

The term "redox state" as thus used herein can be considered to refer to the oxidation-reduction state of any one or more of the three main pyridine nucleotide couples. Each of these couples are:

(A) The cytoplasmic [NAD+]/[NADH] linked dehydrogenase reactions of: (1) Lactate dehydrogenase (EC 1.1.1.27); (2) Maleate dehydrogenase (EC 1.1.1.37); and (3) Glycerol 3-phosphate Dehydrogenase (EC 1.1.1.8).

(B) The mitochondrial [NAD+]/[NADH] linked dehydrogenase reactions of: (1) Beta hydroxybutyrate dehydrogenase (EC 1.1.1.30); and (2) Glutamate dehydrogenase (EC 1.4.1.3).

(C) The cytoplasmic [NADP+]/[NADPH] linked dehydrogenase reactions of: (1) Isocitrate dehydrogenase (EC 1.1.1.42); (2) 6-Phosphogluconate dehydrogenase (EC 1.1.1.44); and (3) Malic Enzyme (EC 1.1.1.40).

The three pyridine nucleotide couples or pools each achieve different redox potentials because of the chemical energies of the substrates to which they are linked by their respective enzymes since the standard redox potential of [NAD+]/[NADH] is about −0.32 V. Thus, the near-equilibrium NAD-linked dehydrogenases have a Keq of about 10^{-11}M, the mitochondrial NAD-linked dehydrogenases have a Keq of about 10^{-9}M, and the cytoplasmic NADP linked dehydrogenases have a Keq of about 1. The differences in pyridine nuclestide redox states within the cell may be considered to result from the fundamental properties of matter. Over time, enzymes have evolved which take advantage of these fundamental properties to organize the chemical reactions of the cell into coherent purposeful sequences we know as metabolism.

The oxidation of lactate anions to pyruvate anions (that is, the loss of $2H^+$ and $2e^-$ from lactate) is accompanied by the reduction of pyridine nucleotide NAD+. That is, NAD+ gains two electrons and one H+ with the other H+ being liberated into the aqueous media where its activity is indicated and controlled by the HCO^-_3/CO_2 couple.

In general, the term "redox state" may also be defined as a ratio of [oxidized substrate]/reduced substrate]. The half or mid point potential Eh is conventionally measured as a potential in volts relative to a standard hydrogen electrode potential in accordance with the Nernst equation. The midpoint potential of the NAD+ system, that is, where the ratio of [NAD+]/[NADH] equals 1 at a pH of 7.0 and a temperature of 25 C. is −0.32 volts under standard conditions. The midpoint potential of $[O^2]/[H_2O]$ is +0.816 volts. The cytoplasmic pyridine nucleotide system accepts H+ and e^- from the organic compounds provided to mammalian organisms and transfers them to the mitochondrial pyridine nucleotide system where, by the electron transfer system, the $2H^+ + 2e^- \xrightarrow{reduce} 1/2O_2$ to form water while conserving the energy of the oxidation reduction reaction by converting ADP+Pi to ATP. The reaction generates energy and heat. The redox state of cytoplasmic [NAD+]/[NADH] couple is about −0.19 volts, that of the mitochondrial [NAD+]/[NADH] couple is about −0.28 volts while that of the cytoplasmic [NADP+]/[NADPH] couple is about −0.42 volts. The last or NADP+ couple is a much stronger reducing agent than the others and is used for reductive synthesis in the body, such as the making of fatty acids from carbohydrates; (see Krebs and Veech, 1969) in *The Energy Levels and Metabolic Control in Mitochondria* (Papa S., Tager J. R., Quagliariello E. & Slater E. C. eds) pp 329-382, Adriatica Editrice, Bari.

In the case of a living cell, a plurality of oxidation-reduction reactions occur simultaneously. Under normal conditions, these reactions occur in a normal healthy cell in a predictable manner. How these various redox states are regulated has just been described in thermodynamic terms. The normal healthy cell keeps the redox state of its free cytoplasmic [NAD+]/[NADH] redox couple at a ratio of about 500 to 1500 which corresponds to a voltage of about −0.2 volts. In this way, the cytoplasmic pyridine nucleotides can accept the H^+ and e^- from the substrates or food presented to the cell so that the cell may convert this food or substrate into energy. When the cell is metabolizing very reduced substrates, such as fatty acids, the cytoplasmic [NAD+]/[NADH] is about 400-800. When the cell is metabolizing carbohydrates or amino acids, it is obvious that these compounds are already partially oxidized. Therefore, the free cytoplasmic [NAD+]/[NADH] reflects the oxidation level of its substrate and becomes more oxidized in the range of about 800 to 1500.

The redox state of the free cytoplasmic [NAD+]/[NADH] couple can be determined by various techniques, such as by measuring the ratio of [lactate−]/[pyruvate−] (a) in freeze clamped tissue, (b) in the venous effluent leaving the organ in question, or (c) in the medium bathing the tissue in question. Alternatively [L-malate−]/[oxaloacetate−] or [-glyerophosphate]/[dihydroxyacetone P] ratios in tissue may be measured, if desired. The valve of cytoplasmic [NAD+]/[NADH] can then be calculated.

In healthy living mammals, the ratio of [L-lactate−]/[pyruvate−] is about 6, but can range, under special situations, such as starvation, to about 15-20. A [L-lactate−]/[pyruvate] ratio below about 20, as occurs after ethanol consumption, because of its links to the cytoplasmic [NAD+]/[NADH], is pathologic. A characteristic in all cells having a low [NAD+]/[NADH] ratio is believed to be demonstrable (observable) pathologic consequences, such as tissue swelling, low phosphorylation potential, low plasma membrane voltage, and abnormal electrolyte distribution between intracellular and extracellular H_2O.

Similarly, the redox state of the free mitochondrial [NAD+]/[NADH] can be determined by various techniques using tissues such as, for example, kidney or liver, by measuring the ratio of [D-beta-hydroxybutyrate−]/[acetoacetate−] (a) in freeze-clamped tissue, (b) in the venous effluent leaving such tissue, or (c) in the fluid bathing isolated such tissues. A determination of the free mitochondrial [NAD+]/[NADH] in other tissues, such as brain or heart muscle, is more complex, but, in some cases, can be accomplished by measurement in freeze clamped tissue of the [alpha-keto glutarate−] [NH4+]/[glutamate−] ratio (see Miller A. L., Hawkins R. A., and Veech R. L.; *J. Neurochem* 20, 1393-1400, 1973).

The normal ratio of mitochondrial [NAD+]/[NADH] is between about 5 and 20, and the normal ratio of [beta-hydroxybutyrate−] 1/[acetoacetate−] is about 1.3 to 4. The value of mitochondrial [NAD+]/[NADH] can then be calculated.

The redox state of the free cytoplasmic [NADP+]/[NADPH] couple is, of course, affected by the [CO_2] of surrounding fluids. Because of the lack of substrates which are permeable to the cell wall without significant and variable gradients, this redox state cannot at present be directly and totally regulated other than by the intracellular metabolic links with the cytoplasmic and mitochondrial [NAD+]/[NADH]. (See Krebs H. A. and Veech R. L.; "Pyridine Nucleotide Interrelations", 1969 in *The Energy Level and Metabolic Control in Mitochondrial* in Papa S., Tager J. M., Quagliariello E., and Slater E. C., eds. pp 329-383, Adriatica Editrice, Bari). Thus, for instance, because pyruvate reacts in both cytoplasmic [NAD+]/[NADH] and [NADP+]/[NADPH], administration of [HCO_3^-]/[CO_2] and [L-lactate−][pyruvate−] within certain narrow limits regulates these ratios because:

$$\frac{[NAD^+]_c}{[NADH]_c} = \frac{[NADP^+]_c}{[NADPH]_c} = \frac{K_{malic\ enzyme} \times [malate^{2-}]}{K_{LDH} \times [L\text{-lactate}^-]\,[CO_2]}$$

Pyruvate, L-lactate and CO_2 are permeable to cell wall in a simple fashion, as are D-betahydroxybutyrate and acetoacetate, while malate^{2-} and other dicarboxylates are not.

While the importance of redox state to the maintenance and normalization of intracellular metabolic processes and bioenergetics has long been recognized, there has never been previously, so far as is now known, any attempt to regulate or to normalize the redox state in such mammals (including especially human patients) receiving intravenous therapy, in patients undergoing dialysis, or in patients receiving parenteral nutrition. The present invention provides compositions and methods for regulating and/or normalizing the redox state in mammals (including man) treated herewith.

Existing electrolyte fluids make no attempt to maintain or normalize cellular redox potentials in any way whatsoever. In fact, most existing electrolyte fluids actually severely distort or make abnormal the redox balance of the cells, resulting in multiple and definable abnormalities. In this way, existing electrolyte fluids distort, such things as, for example, the rate of fat oxidation, the rate of glucose production, the rate of uric acid excretion, the rate of galactose metabolism in milk fed infants, and the like. All of these abnormalities lead to respectively, accumulation of fat in tissue, such as, for example, liver, production of either hyperglycemia or hypoglycemia, gouty crisis, cataracts, and neurological damage.

B. The Phosphorylation Potential

Just as the [NAD+]/[NADH] ratio is defined as a "redox state", by analogy, it is customary to define the energy state of the adenine nucleotide co-enzyme couple as the "phosphorylation potential". Because in living cells ATP, ADP, and HPO_4 exist in several charged forms, and in various complexation states with Mg^{2+}, it is customary to define these forms as sigma ATP, sigma ADP, and sigma Pi. The phosphorylation potential is thus defined by the relationship [sigma ATP]/[sigma ADP][sigma Pi].

It is clear that the reaction of oxidative phosphorylation contains both the redox state of mitochondria and the cytoplasmic phosphorylation potential. While the phosphorylation potential cannot apparently be controlled directly by addition of ATP and ADP to fluids contacting cells, since these compounds do not penetrate cell wall, there is, however, another reaction which is in near-equilibrium with the cytoplasmic [sigma ATP]/[sigma ADP][sigma Pi] (see Veech et al. in *J. Biol. Chem.* 254, 6538-6547, 1979). The reaction involves the two most active enzymes in the glycolytic sequence found in nearly all living cells and catalyzed by the enzymes glyceraldehyde 3-phosphate kinase (EC 2.7.2.3). Veech et al. (reference just cited) provide an equation which defines the relationship between the free cytoplasmic [NAD+]/[NADH] or redox state and the cytoplasmic phosphorylation state or [sigma ATP]/[sigma ADP] [sigma Pi]. This relationship is now and accepted by those familiar with this art and is (equation 5):

$$K_{G+G} = \frac{[\text{sigma 3-PG}][\text{sigma ATP}]}{[\text{sigma GAP}][\text{sigma ADP}][\text{sigma Pi}]} \cdot \frac{[NADH][H^+]}{[NAD+]} = 1.83 \times 10^{-4}$$

or

$$\frac{K_{G+G}}{K_{LDH}} = \frac{[\text{sigma 3-PG}]}{[\text{sigma DHAP}]/22} \cdot \frac{[\text{sigma ATP}]}{[\text{sigma ADP}][\text{sigma Pi}]}.$$

-continued

$$\frac{[\text{l-lactate}]}{[\text{pyruvate}]} = 1.65 \times 10^{+7}\,M^{-1}$$

Metabolism in any living cell may be considered to be an ordered process whereby [H+] and electrons [e−] are removed from substrates and passed to co-enzyme acceptors which are largely cytoplasmic NAD+. This co-factor thus has a potential in the cell for more oxidation at about −0.19 volts than its standard potential of about −0.32 volts so that it may accept these electrons. The H+ and e− gathered in the cytoplasm, or even created in the mitochondria, may then be transferred to mitochondria by mechanisms involving other substrates to mitochondrial NADH which has a lower potential of about −0.28 volts in most mammalian cells. If e− and H+ are produced with a higher voltage, such as for example, from the oxidation of succinate or fatty acids, they form reduced FADH2 from FAD which has a more oxidized potential and therefore less potential energy. H+ and electrons produced from NADH-linked substrates produce 3 ATP for each ½ O_2 consumed while those from flavo-protein (FAD) acceptors produce only 2. This difference in energy is due to the fundamental difference in the chemical reactions involved in producing the H+ and e−.

The fundamental process of cell respiration where NADH is oxidized to form heat and energy is called oxidative phosphorylation. It occurs in cellular organelles called mitochondria in a series of redox reactions called the electron transport chain. The mitochondrial electron transport system takes two electrons [2e−] from substrates and passes them up the chain to reduce ½ O_2 forming H_2O. The energy realized in this process is conserved in the cell in a chemical form of anhydride bond in the terminal phosphate group of adenosine triphosphate (ATP). The formation of three pyrophosphate bonds of ATP leads to the formation of H_2O and requires 3H+ in addition to the formation of the $1H_2O$ formed from NADH plus H+ plus 2 e− taken from the substrates being oxidized by the cell. The reaction of oxidative phosphorylation is a spontaneous one (see Veech et al in cited reference).

The phosphorylation potential of living cells can be measured by determining the cellular contents of the components of certain metabolites (see Veech R. L., in *J. Biol. Chem.* 254, 6538-6547, 1979). In certain tissues, such as brain, heart, or skeletal muscle, measurement of the components of the creatine kinase reaction (EC 2.7.3.2) may be used as the preceding reference describes.

Since on theoretical grounds Veech et al. in *J. Biol. Chem.* 254, 6538-6547, 1979 showed that [creatine]/[creatine-P] is in near equilibrium with the cytoplasmic [sigma ATP]/[sigma ADP], it follows that the phosphorylation potential in skeletal muscle or brain may be evaluated in living human patients by measuring the [sigma CrP]/[Sigma Pi] ratio without resorting to freeze-clamping of organs by the use of ^{31}P NMR (nuclear-magnetic residence) as has been done by Chance and others (see Chance B., et al., *Proc. Nat'l. Acad. Sci.* U.S. 78, 6714-6718, 1981). The agreement between the necessarily destructive methods heretofore used in animals by Veech, and the somewhat less precise but nonharmful methods of sigma creatine-P/sigma Pi measurements with ^{31}P NMR, demonstrate that the normal value of the phosphorylation potential or [sigma ATP]/[sigma ADP][sigma Pi] as estimated by Veech is essentially correct (as stated above). Further, the increasing availability of ^{31}P NMR facilities in academic medical centers ensures that measurements in living human patients can be conducted without harming them.

Because the cytoplasmic [sigma ATP]/[sigma ADP]-[sigma Pi] or phosphorylation potential is related to the cytoplasmic [NAD+]/[NADH] or redox state by a near-equilibrium reaction catalyzed by glyceraldehyde-3-phosphate dehydrogenase and 3-phosphorglycerate kinase, it is possible to alter and regulate and normalize the phosphorylation potential of a living cell by affecting its redox state (as is believed to be accomplished in the present invention).

If a simple, reliable chemical means are known and/or could be devised to change the intracellular redox state, it would of necessity have to change the other components of the reaction which include the phosphorylation potential and would be of obvious fundamental importance in medicine and in many other related fields of biochemistry, physiology, molecular biology, tissue culture, veterinary medicine, and like endeavors. Such a chemical means is provided by the teachings of the present invention.

C. Redox Active Metabolites

As above indicated, a large portion of metabolism is devoted to energy generation which involves the removal of H+ and e− from substrates in cytoplasm or mitochondria for delivery to mitochondrial electron transport scheme for conversion of 2H+ plus 2e− with ½O_2 to yield H_2O with the liberation of about 1 volt or 54 Kcal/mole of energy which is conserved in the [sigma ATP]/[sigma ADP][sigma Pi] couple. In mammalian cells, the [sigma ATP]/[sigma ADP][sigma Pi] has a delta G (free energy in kilocalories per mole) of between −13.6 and −14.1 Kcal/mole, the transfer to this H+ and e− is accomplished by a series of cofactors, the major one being NAD (nicotinamide adenine dinucleotide) and its phosphate (called NADP). Oxidation is defined as the removal of electrons, and reduction as the addition of electrons. The removal or addition of e− plus H+ from substrates is catalyzed by enzymes, the major group of which are called dehydrogenases, as indicated above. The enzymes (catalysts) control the rates at which reactions occur, but the extent and the direction of a reaction, and the amount of energy (delta G) which may be liberated by a reaction, is determined by the inherent energy in the chemical bonds (delta G°) and the concentrations of the reactants and products.

Determination of any redox or energy state must always involve a ratio of chemical compounds, [oxidized product]/[reduced reactant] and [oxidized co-factor]/[reduced co-factor]. The overall reaction is thus comprised of two individual redox systems, one of which is oxidized, while the other is reduced.

Those enzymes within a cell which are of sufficiently high activity relative to the flux through the enzyme to catalyze a state of near equilibrium are suitable for controlling the redox state. A reaction may be experimentally determined to be in a state of near-equilibrium by measuring the equilibrium constant (Keq) under conditions which approximate those existing within a cell, that is, where the ionic strength I equals 0.25, the pH equals 7 to 7.2, the temperature equals 38° C., and the free [Mg^{2+}] equals 0.5 to 1 mM, and also where I equals ½ sigma molarity of ions times the valence of ions. With

knowledge of the value of Keq, the concentration of the reactants in a tissue may be measured in rapidly frozen tissue. If the value of [product]/[reactant] measured, in several different dehydrogenase reactions, gives the same calculated free $[NAD(P)^+]/[NAD(P)H]$ ratio, then the reaction is said to be in "near-equilibrium" under in vivo conditions. In the case of near-equilibrium dehydrogenase reactions, addition of a predetermined amount of a ratio of product/reactant allows one to set the $[NAD^+]/[NADH]$ ratio within the cell at a predetermined level, provided the reactants penetrate the cell wall freely or in a constant ratio one to another. The redox state or $[NAD(P)]^+/[NAD(P)H]$ ratio may be set inside a cell by controlling the $[CO_2]$ and the redox state of the cytoplasmic free $[NAD^+]/[NADH]$ as described previously. Each of the three couples employed in this invention is a near equilibrium couple.

Various cytoplasmic and mitochondrial NAD-linked dehydrogenases appear to be capable of controlling or setting the $[NAD^+]/[NADH]$ ratio in each of cytoplasm and mitochondria. Because of the special permeability of the complete couple of L-lactate$^-$/pyruvate$^-$ for cytoplasm and D-B-hydroxybutyrate$^-$/acetoacetate for mitochondria, these two redox couples are preeminently well suited for the practice of this invention. This is so because: (1) both monovalent anions in the pair distribute themselves equally between plasma and cellular H_2O; (2) changes in distribution of anions between extracellular and intracellular H_2O during pathological states will effect both members of the couple equally through preserving the integrity of the given redox state; (3) both couples react with "dead end" branches off the main metabolic sequences; (4) the concentration of these normal transport metabolites can reach very high levels in plasma of normal healthy mammals under physiological conditions; and (5) the members of both couples each contain a charge which can be used to normalize the low Na^+:Cl^- milliequivalent ratio characteristic of most I.V. (intravenous) solutions.

The near equilibrium redox active metabolite carboxylate couples employed in the practice of the present invention, specifically, l-lactate$^-$/pyruvate$^-$ and d-betahydroxybutyrate$^-$/acetoacetate$^-$, constitute safe entry points and appear to be unusual in their ability to not only normalize the redox state in cytoplasm through the reaction of l-lactate and pyruvate with LDH, but also to regulate the redox state in the mitochondria through reaction of and d-betahydroxybutyrate and acetoacetate with the enzyme d-betahydroxybutyrate dehydrogenase (EC 1.1.1.30) which is apparently present in most tissues at a high enough activity to maintain near-equilibrium conditions at most times.

As indicated above (see Table 1 and related text), previous attempts to normalize the sodium to chloride milliequivalent mole ratio of about 1.36 were usually done by adding either (d,l) lactate$^-$ or acetate$^-$, or a combination of lactate and acetate, or other inappropriately paired carboxylate anions, leading inevitably in all known instances to severe and measurable pathological consequences.

In the solutions of the present invention, one employs at least one of the above indicated three different near-equilibrium couple mixtures. In each couple mixture, the two member components are employed in a definite milliequivalent ratio relative to ne another. Such a ratio is needed in order to control either the plasma pH, or the redox state (and consequently the phosphorylation potential), or both.

Among the possible mixture couples which could be used, these three couples were selected because, for each couple:

1. The distribution of ions between extracellular fluid and intracellular fluid is predictable in all normal and pathological states.
2. It is capable of achieving and regulating a predetermined redox state and phosphorylation potential within most living cells.
3. At least one member thereof contains an anionic charge.
4. It can be given in aqueous solution form so that the total levels administered do not substantially exceed total levels found under normal physiologic conditions in mammalian blood (plasma).
5. Both members thereof constitute safe entry points which enter the metabolic sequence and pathways at a safe entry point and these safe entry points, are at dead end terminals in the metabolic pathways, thus avoiding any possibility of a pathologic buildup of metabolites with the consequence that a disordering of cellular metabolism would consequently result.
6. It need not induce a change in water distribution between intracellular and extracellular space.
7. It may be osmotically neutral in most tissues.
8. Administration permits control of water distribution as a result of changing redox and hence the linked phosphorylation state and the magnitude of the extracellular Na^+ Donnan forces generated thereby.

When blood levels of, respectively, l-lactate/pyruvate, d-betahydroxybutyrate/acetoacetate, and bicarbonate/CO_2 are maintained within their normal limits, then the redox state, the phosphorylation state, and the plasma pH each tend to be normalized which is achieved as a result of administration of a solution of this invention.

Intracellular concentration of each member of each coupled is achieved through the extracellular fluid because each of the monovalent anions chosen, namely, l-lactate and pyruvate, d-betahydroxybutyrate, and acetoacetate, and also bicarbonate, distribute themselves between plasma water, extracellular water, and intracellular water in concentration ratios or gradients which are the inverse of the hydrogen ion (concentration), thereby achieving a gradient or ratio of about 1.35 between extracellular and intracellular fluid. The nonionic dissolved CO_2 distributes itself substantially equally between extracellular fluid and intracellular fluid.

Those learned in the art realize a redox state must be defined at a certain pH, or $[H^+]$ ion concentration. The near-equilibrium couple $[HCO_3^-]/[CO_2]$ defines the cellular pH or $[H^+]$ concentration. This near-equilibrium couple is therefore an integral part of the redox state. Preferably the level of sigma $[HCO_3^-]$ plus $[CO_2]$ present in any given solution of this invention may vary under normal physiological conditions from about 10 mM/l to 40 mM/l, but in general, is (when present) in the range from about 25 to 35 mM/l. The milliequivalent ratio of $[HCO_3]/[CO_2]$, of course, in effect, is defined so as to give a $[H^+]$ ion concentration, or pH, in the physiological range as defined above.

The redox and phosphorylation states in various tissues in the rat have been given by Veech et al. *J. Biol.*

Chem. 254, 6538-6547, 1979 and for the redox states in Veech, Eggleston and Krebs, *Biochem. J.*, 115, 609-619, 1969. The same general principles are believed to hold for man, but cannot be directly proved since freeze clamping is not possible. NMR measured estimates of the phosphorylation potential in brain and muscle in living humans, however, agree well with these figures derived by freeze clamping procedures.

By the term "plasma" or "blood plasma" as used herein, conventional general reference is had to the liquid part of the blood as distinguished from the corpuscles. Plasma can be prepared by various techniques well known to those familiar with this art typically using centrifugal force to separate a supernatant (which is plasma) after non-coagulated blood is centrifuged.

By the term "extracellular fluid" as used herein conventional general reference is had to all body fluids in extracellular spaces outside of the circulatory system (e.g. the blood) and outside of intracellular fluid in a mammal (typically constituting about 15% of the weight of a mammal).

By the term "intracellular fluid" as used herein conventional general reference is had the fluid within cells which constitutes about 57% of total mammalian body weight.

It is well known that (see Black DAK. *Lancet i*, 305-12 1953) infusions into a mammal of large amounts sodium and chloride in a solution milliequivalent ratio of 1 to 1 lead inherently to hyperchloremic acidoses. This knowledge lead to the development of such well known solutions as lactated Ringers, and also to the compositions used in most dialysis solutions, wherein, in a majority of cases, the sodium to chloride milliequivalent ratio is normalized compared to plasma values by the addition of various organic anions (as described above). These organic anions chosen in the prior art are as described above. In no known prior art case, however, were any solutions with a normalized Na:Cl milliequivalent ratio produced which did not use organic ions in such a way as to inherently lead to severe and measurable metabolic abnormalities and pathologic consequences. Mixtures of redox pairs nor HCO_3^-/CO_2 were not generally used to normalize the $Na^+:Cl^-$ ratio nor were the reasons known why a choice of near equilibrium matched couples was desirable. Correction of this ratio between sodium cation and chloride anion by the mixture couples as taught by the present invention eliminates the pathologic consequences of all the prior art electrolyte solution compositions. In addition, the solution compositions of this invention tend to normalize plasma inorganic electrolyte composition and to correct the anion gap which in many instances could not be accomplished by prior art electrolyte solutions.

Thus, in summary, the compositions of this invention tend to normalize (a) plasma pH, (b) composition of major plasma inorganic electrolytes, (including the milliequivalent ratio of $Na^+:Cl^-$ and the anion gap), (c) the redox state, and (d) the phosphorylation potential. These normalizations are obtained and achieved without the abnormal, pathological consequences inherent in all known prior art solutions. No other man-made solutions are presently known which will accomplish this combination of results.

D. Other Possible Benefits (Theorized)

It is theorized, and there is no intent to be bound by theory herein, that the solutions of the present invention, in addition to the properties above described, further tend to normalize at least one of the following states:

1. Distribution of water between intracellular and extracellular compartments,
2. Distribution of major inorganic electrolytes between intracellular and extracellular fluid,
3. Transmembrane cellular potential, and
4. The degree of organization within the living cell or its entropy.

The ratio of the chemical activity of free water on each side of a typical normal mammalian cell membrane is always unity. Movement of water across such a cell membrane is achieved by the movement of osmotically active substances. Changing the cellular phosphorylation potential, through the NaK ATPase, therefore, inherently effects a change in the steady state level of ions inside and ions outside of a cell with the net result being a change in the level of osmotically active substances on either side of the cell membrane.

The transmembrane cellular potential is herein viewed as a Donnan potential (see Donnan F. G., *Chem. Rev.* 1, 73-90, 1924) resulting from the total amount of the non-diffusible osmotically active substances on either side of the cell membrane, and so is not a function of the so-called electrogenic sodium potassium ATPase, as is commonly held. (See *The Cell* (1983), Alberts B., Bray D., Lewis J., Raff M., Roberts K. and Watson J. D., pp 294, Garland, N.Y.). Rather the Na/K ATPase is viewed as an electroneutral "osmopump" exporting a net of 2 milliosmoles (1 Na^+ and 1 Cl^-) from intracellular to extracellular space for each ATP by hydrolyzed. The distribution of $[Na^+]$, $[K^+]$, $[Cl^-]$ and $[Ca^{2+}]$ in most extracellular and intracellular fluid is thus viewed as a function of the phosphorylation potential and the state of internal cellular order or entropy. The NaK ATPase is thus viewed as the near-equilibrium link between intra and extracellular electrolytes in the manner given in equation 7. The magnitude of the extracellular fluid Na^+ Donnan is therefore a function of the cellular phosphorylation state. (See Leaf A. *Biochem J.* 62: 241-248, 1956)

Cellular water volume can be measured by known (e.g. conventional) techniques involving the distribution of inulin and tritiated water.

Distribution of major inorganic electrolytes between intracellular and extracellular fluid can be measured by known (e.g. conventional) techniques, such as flame photometry, atomic absorption spectroscopy, van Slyke gas analysis, and the like.

Transmembrane cellular potential can be measured by known (e.g. conventional) techniques; such as with electrodes or probes, and the like. Calculation of such cellular voltage can be achieved from a measurement of the distribution of chloride ions between intracellular and extracellular fluid following Nernst's law.

A quantitative relationship is theorized to exist involving redox state, phosphorylation potential and the above referenced three states. This relationship may be expressed by the following equation:

$$\Delta G = o = \Delta G^{\circ}_{ATPase} + \Delta G^{\circ} \frac{[Na^+]\ldots}{[Na+]\ldots} + \quad (7.)$$

$$RT \ln \frac{[\Sigma ADP][\Sigma Pi]}{[\Sigma ATP]} +$$

-continued

$$RT \ln \frac{[Na^+]_o^3 [K^+]_i^2 [Cl^-]_o}{[Na^+]_i^3 [K^+]_o^2 [Cl^-]_i} + T\Delta S$$

wherein

The values of the various terms in the foregoing equation of are given as follows (for muscle and brain):

$$\Delta G = 0 = -7.73 \text{ kcal/mol} + 0 + (-6.3 \text{ kcal/mol}) + 8.4 \text{ kcal/mol} + 5.6 \text{ kcal/mol} \quad (7.1)$$

In the foregoing equation, the phosphorylation potential is shown to be in a state of near equilibrium with the substrates of the sodium potassium ATPase. Since the chloride ion is cell wall permeable, this ion distributes itself in conformity with the transmembrane cellular potential. Movement of three sodium ions out of the cell and two potassium ions into the cell across the cell membrane necessarily results, from the law of electrical neutrality, in the movement of one chloride ion from inside the cell to outside the cell across the cell membrane. This makes the sodium potassium ATPase, in effect, an osmopump resulting in the export of two millisomoles per ATP hydrolyzed. This pump is electro-neutral.

The T delta S term, which is approximately 5.6 kilocalories per mole of ATP hydrolyzed, is an entropy term. It, therefore, refers the state of randomness within the cell. The positive nature of this entropy term indicates that a high degree of order is imposed on the intracellular environment. In terms of quantum and statistical mechanics, the number of ways of achieving a certain energy state is called its degeneracy (Ω). The Boltzmann equation defines S (or entropy) as $S = K_B \ln \Omega$, where Boltzmann's constant (which relates the gas constant to Avogadro's number), or $K_B = 1.38 \times 10^{-23} J/°K$.

It follows from the foregoing equation 7, above, that the distribution of calcium inside the cell is a function of the cube of the respective sodium concentrations inside and outside of the cell because of the action of the high-activity sodium-calcium exchange enzyme. The following equation shows the relationship:

$$K_{Na/Ca} = \frac{[Na^+]_i^3 [Ca^{2+}]_o [Cl^-]_i}{[Na+]_o^3 [Ca2+]_i [Cl-]_o}$$

where:

$[\,]_i$ ~intracellular concentration in cytoplasmic H_2O

$[\,]_o$ ~concentration in extracellular H_2O.

Unlike the simple NaK ATPase which moves 2 mOsmoles out of the cell thus moving H_2O with it, the result of moving Ca^{2+} out of the cell by the Na-Ca exchanger is to move a net of 3 mOsmoles into the cell, thus increasing the cells water content. The NaK ATPase must then operate again to move the excess sodium out in exchange for K^+ to restore osmotic equilibrium between extracellular space H_2O and cell H_2O.

The net result of the foregoing equation (7) is that the water of both intracellular and extracellular fluid is a function of the sodium/potassium ATPase (EC 3.6.1.3) and also of the phosphorylation potential.

It can be empirically seen that the voltage across a cell membrane is inversely related to the chloride distribution and the phosphorylation potential.

Correlation between phosphorylation potential, intracellular chloride and transmembrane cellular potential for various mammalian tissues is illustrated in Table II below:

TABLE IIa

Correlation between Phosphorylation Potential, Intracellular Chloride and Transmembrane Cellular Potential.

	$\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]}$	$[Cl^-]_i$ mEq/l	ΔE mV
red cell	7,000	90	−9
liver	15,000	40	−40
brain or muscle	30,000	7-9	−70

From Table II, it is seen that low phosphorylation potential correlates with a high intracellular chloride, and a low transmembrane cellular potential correlates with the inherent setting of the potential as a function of the Donnan-active material within the cell with the phosphorylation potential merely overcoming the Donnan forces so as to export two milliosmoles, as described in equation 7.

Because of the voltage dependent permeant nature of chloride ion to most non-epithelial tissues (Ho MK, Guidotti G. *J Biol Chem* 250: 675-683, 1975) the induction of high extra cellular chloride, such as occurs, for example, in current intravenous electrolyte therapy, must have profound pathological consequences for the metabolism of the cell, even though the purpose of such intravenous and dialysis therapy is to normalize the water and electrolyte concentrations of the various mammalian body cellular compartments. This is so because the ratio

$$\frac{[Na^+]_o^3 [K^+]_i^2 [Cl^-]_o}{[Na^+]_i^3 [K^+]_o^2 [Cl^-]_i}$$

and the $T\Delta S$ term link the cellular phosphorylation and the cellular redox states to intracellular and extracellular water and the electrolyte concentrations of Na^+, K^+, Cl^- and also Ca^{2+}.

E. Electrolyte Solution Preparation

The electrolyte solutions of the present invention can be prepared by any convenient or conventional procedure.

As a matter of accuracy, the compositions of this invention can be described in terms of their ion contents which can be expressed either in terms of millimoles per liter of solution, or milliequivalents per liter of solution. It is standard practice in this art in describing a given solution to separate anions from cations, and nonionics from ionic materials; this practice is followed herein in the main. As those skilled in the art will readily appreciate, a translation or conversion of millimoles per liter of solution, or of milliequivalents per liter of solution, into grams of a given salt added per liter of water is routine and is given in any standard text book in the field, such as, for example, "Data For Biochemical Research" (1969) (Dawson R. M. C., Elliott W. H., Jones K. M., Eds.) Clarendon Press, Oxford at pages 507 and 508. This reference illustrates not only the salt starting materials, but also the order of addition of same in the preparation of certain illustrative prior art electrolyte solutions shown therein. Solutions of this invention are readily prepared by this type of procedure. The particular salt combination used for a given solution may change from time to time in a manufacturing operation as those skilled in the art well know. The significant

factor is that the final concentrations of respective component ions in any given solution remain as specified or desired. In view of the developed state of this art, no detailed description of electrolyte solution preparation procedure is believed to be necessary or desirable herein.

The solutions of this invention, and the component materials incorporated thereinto, are, in general, formulated, so as to contain a combination of a the desired physiological Na^+:Cl^- milliequivalent ratio normality, one or more of these three near-equilibrium couple(s), and other components.

Thus, various initially existing pathological conditions can be ameliorated by practice of the processes and the compositions of the present invention, depending upon the particular solution used and the particular use conditions and circumstances in any given use situation. Thus, by this practice of this invention, one can accomplish in a physiologically acceptable manner the removable of metabolic products from cellular water, the replacement of body fluids and electrolytes, and the administration of nutrients, and the like, as desired. The solutions may be administered in any fashion desired so long as they contact living mammalian tissue. Administration can be accomplished by any convenient technique, such as for examples, intravenously, intraarterially, intradermally, intrathecally, orally (especially when the solution contains the non-bicarbonate containing couples), across a semi-permeable membrane, or the like, as those skilled in the art will readily appreciate. The solutions of this invention as prepared are, in general, well suited for the administration of therapeutic agents to living mammals.

When bicarbonate anions are not present, then the level of combined (or sigma) l-lactate/pyruvate and/or d-betahydroxybutyrate/acetoacetate present in a solution of this invention is optionally greater than when bicarbonate is present in order to achieve the desired milliequivalent ratio of sodium to chloride, as indicated. The concentration of either sigma l-lactate/pyruvate and/or of d-betahydroxybutyrate/acetoacetate in a given solution of this invention can thus range up to the full maximum quantity desired (within the limits described herein). It is presently preferred, particularly when no bicarbonate is present, to employ a mixture of l-lactate/pyruvate with a mixture of d-betahydroxybutyrate/acetoacetate.

Those skilled in the art will realize that in any given solution of this invention one can incorporate an excess of one or more individual members of any one mixture couple of this invention so that (a) the ratio of one member to the other of any given couple and (b) the total quantity of both mixtures or members lies outside of the ranges hereinabove described without departing from the spirit or scope of the invention. Such a single member excess is not recommended when practicing the present invention. However, if such a single member excess does occur, the amount of the excess can be calculated by determining the maximum ratio of one couple member to the other which can be present in accord with the above teachings, and then the quantity of one couple member remaining (or present) which is outside of this ratio range may be considered to constitute an excess. The effect of such an excess is evidently merely to cut down, but not to eliminate, the efficacy of what effect would otherwise be obtained by using only a solution which contains mole ratios and quantities of respective mixture couples within the spirit and scope teachings of this invention.

In the making of solutions of this invention, it is preferred to employ the optically active l-lactate salts or l-lactic acid (which will make the desired l-lactate anions in solution), and also similarly to employ d-betahydroxybutyric acid or d-betahydroxybutyrate salts (which will make the desired d-betahydroxybutyrate anions in solution. Choice of particular salt or acid (or mixture) used in any given case depends among various factors, such as upon the other starting inorganic salts which a formulator desires to use (based upon availability, cost, and like factors), all as will be readily appreciated by those skilled in the art. Racemic (d-l) mixtures could be used, but their use is preferably avoided since these unnatural isomers are known to be associated with specific toxic effects. Racemates can be metabolized. If such are used, the ratios of one member to another in the respective near equilibrium couples involved should be based upon the quantity of particular optically active form present (e.g. either [l-lactate$^-$] or [d-betahydroxybutyrate$^-$], as the case may be.

In the solutions of this invention at the pH ranges described, not all couple member material of any given couple will be in an ionized (anionic or dissociated) form; a portion of this material will be in an un-ionized (undissociated) form. Typically, the quantity of undissociated material (such as l-lactate acid, pyruvic acid, d-betahydroxybutyric acid, acetoacetic, sodium bicarbonate, carbonic acid, or the like) is not more than about 0.1% of the total quantity of all material of any given species (e.g. l-lactate, pyruvate, d-betahydroxybutyrate, acetoacetate, or bicarbonate). For purposes of calculating a milliequivalent ratio, molar concentration, or the like, it is preferred to base computations upon the total material of any given species which is present in a solution of this invention.

The carbon dioxide, when used, can be introduced either as a gas, preferably using conventional aeration apparatus to effect a solubilization of CO_2 in a solution, or it can be generated in situ from a dissolved metal (such as sodium preferred), potassium, calcium or magnesium) salt of bicarbonate in combination with a dissolved acid (lactic, pyruvic, betahydroxybutyric, or acetoacetic) in respective proportions of each such that the total quantity of dissolved carbon dioxide so generated is within the ranges described herein for use in a solution of this invention.

As elsewhere indicated herein, if desired, a solution of this invention can also contain various known additives in concentrations taught by this art, but it is presently preferred not to employ anions and nonionics which will not be safe entry points.

In general, a solution of this invention should contain as a minimum of total of sigma (lactate/pyruvate and/or sigma betahydroxybutyrate/acetoacetate) and/or sigma bicarbonate/carbon dioxide which is at least about 0.5 millimoles per liter as indicated. Below these levels, benefits in normalization of body metabolism as explained above are apparently achievable, but such benefits become increasingly difficult to demonstrate and prove by state of the art techniques of measurement. Consequently, it is preferred to avoid, if possible, homeopathic possibilities by using minimum concentrations as above indicated.

When bicarbonate is present, the total quantity of sigma (lactate/pyruvate and/or betahydroxybutyrate/acetoacetate) used can generally be reduced

which is now believed to be desirable. Thus, when bicarbonate is present, the total sigma (l-lactate/pyruvate and/or d-betahydroxybutyrate/acetoacetate) is preferably about 2 to 17 millimoles per liter.

When a solution of this invention contains at least one osmotically active substance (preferably metabolizable and nonionic), it is added to provide nutritional or osmotic requirements. Since it is uncharged, it does not therefore contribute to normalizing the Na^+:Cl^- ratio or to correcting the anion gap.

F. Classification and Usage of Electrolyte Solutions

All of the formulations of this invention from a composition viewpoint fall into what can be regarded generally as being either one of two distinct classes:

Class I which comprises fluids containing at least one and not more than two metallic cations selected from the group consisting of sodium, potassium, calcium and magnesium, while

Class II which comprises solutions containing at least three and typically not more than four metallic cations selected from the same group.

Class I fluids are typically administered at dose levels which are not greater than about 1 liter per human adult patient per 24 hour day, one typical dose level being 500 ml per such patient per 24 hour day.

Class II fluids are typically administered at dose levels chosen by the physician, and these levels can range from 0 to greater than 100 liters per human adult patient per 24 hour day, depending upon circumstances.

Each of the inorganic electrolytes present in a solution of this invention is typically present in an amount of at least about 0.5 mM/l thus clearly qualifying them as "electrolytes" as such rather than as trace metals, such as is associated with levels of iron, manganese, zinc and the like in normal plasma and which trace metals can be present in normal plasma at levels less than about 0.4 mM/l. If desired, of course, trace materials can be added to solutions of this invention.

Each of the cations sodium, potassium, calcium, and magnesium and each of the anions bicarbonate, chloride, and phosphate are normally found in the plasma and tissue of mammals at concentration levels greater than or equal to about 1 millimolar per liter of body fluid (see Table I). The solutions of this invention, in general, contain respective inorganic electrolyte concentrations which resemble the corresponding concentrations of such electrolytes in plasma (when any one of such electrolytes is present in any given solution of this invention).

Class I solutions are useful as intravenous solutions for electrolyte and fluid therapy especially where no more than about 10% of total blood volume (about 500 ml in an adult human) is to be administered over a 24 hour day. Solutions of this type have been used in the treatment of hemorrhagic shock where 2400 mOsmolar NaCl solutions have been advocated. (See Velosco IT, Pontieri V, Rocha M, Silva E, Lopes OU. *Am J Physiol* 239: H664–673, 1980).

Class II solutions find use in intravenous applications where over 10% of total blood volume (about 500 ml in an adult human) is needed to be given to a human adult over a 24 hour day. Administration can be made, for example, to a normal human with an impairment or injury, such as loss f limb or the like, or to a human with impaired rental excretion: Class II solutions can be used as a improvement for lactated Ringer's solution.

Class II solutions also are useful in dialysis, peritoneal, ambulatory peritoneal dialysis or hemodialysis, where perhaps 120–160 liters per hemodialysis day per patient are used. Such solutions can be used improve existing acetate or lactate containing solutions, but use of acetate is not desired in the practice of this invention.

Given the solutions of this invention, a physician may henceforth wish to administer normal or hypertonic saline solution only to correct a condition of metabolic alkalosis since giving Na^+:Cl^- in a 1:1 milliequivalent ratio causes acidosis and other disturbances recognized herein. The solutions described herein improve normal saline solution.

Solutions of Class II can be used as such, or can be employed as diluent for plasma extenders or for reconstituted frozen blood. For example, dehydrated plasma can be dissolved and dispersed in a solution of Class II so as to produce an injectable solution, as those familiar with the art will appreciate.

Each one of these Class I and II solutions can be considered to be characteristically comprised of four subgroups which can be stated briefly as follows:

A. Solutions containing only inorganic ions and one or more of our near-equilibrium couples of organic anions pairs with which chloride anions are included.

B. Solutions containing in addition to such inorganic ions and organic ion pairs a mixture of bicarbonate and carbon dioxide.

C. Solutions containing such inorganic ions and organic ion pairs plus non ionic materials.

D. Solutions containing in addition to the inorganic ionic material both mixtures of bicarbonate and carbon dioxide (as characterized in B above) plus other nonionics (of the type characterized in C above).

As indicated above, avoidance of substances in solutions of this invention which do not constitute safe entry points is preferred. For example, use of such nonionic osmotically active substances as fructose and glycerol are preferably avoided and are not recommended for use in the practice of this invention. Also, avoidance of the organic anions used in the prior art which are not safe entry points is recommended, including use of lactate alone, acetate alone, lactate and acetate together, gluconate, citrate, and the like.

Prior art in dialysis fluids shows that the composition of the fluids now commercially used evidently is intended to approximate that of plasma with the proviso that the anion gap is typically corrected with abnormal amounts of typically acetate or lactate. The suggestion has also been made in the prior art dialysis fluid composition should approximate the composition of interstitial (extracellular) fluid. While such compositional approximations now appear to be essentially incorrect especially from the standpoint of achieving dialysis fluids of maximal safety and utility and patient benefit, it is submitted that such approximations can be substantially benefited by compounding dialysis solutions in accord with the teachings of the present invention (both for hemo- and peritoneal dialysis).

Solution compositions of the present invention of Class I and Class II are generically characterized herein above. The following Table III summarizes preferred solutions of this inventi n in terms of composition at the time of administration (e.g., water having dissolved therein each of the indicated components in the respective amounts indicated).

1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14 - 20

With regard to the term "nonionics" in a solution or process of this invention, those skilled in the art will appreciate that this term connotes no net charge on the molecule involved at the particular solution pH specified.

Solutions of this invention can be prepared as concentrates which at 0.8 molar solutes or greater will inhibit bacterial growth, as those skilled in the art will appreciate, and such concentrates can then be diluted with water before administration to prepare compositions of this invention.

In general, solutions of this invention are believed to be preparable so as to be storage stable for periods of time at least sufficient to permit packaging, intermediate storage in sealed containers, followed by administration.

TABLE III

Generic Compositions of Class I and Class II Solutions

Component	Composition of time of Administration Quantity Range (millimoles per liter) broad	preferred
Total cations (mEq/L)	1 to about 2400	130 to 170
(1) sodium$^+$	1 to about 2400	130 to 165
(2) potassium$^+$	0 to about 90	0 to 5
(3) calcium^{++}	0 to about 60	0 to 1.5
(4) magnesium^{++}	0 to about 15	0 to 1
Total anions (mEq/L)	about 1 to 2400	130 to 170
(5) chloride$^-$	0.6 to about 1940	80 to 130
(6) bicarbonate$^-$	0 to about 465	0 to 60
(7) sigma l-lactate$^-$/ plus pyruvate$^-$	0 to about 465	0 to 60
(8) sigma d-betahydroxy-butyrate$^-$/plus acetoacetate$^-$	0 to about 465	0 to 60
(9) sigma (6 + 7 + 8)	0.1 to about 465	25 to 65
Total nonionics	0 to about 2400	0 to 305
(10) carbon dioxide	0 to about 25	1 to 5
(11) osmotically active substances*	0 to about 2400	0 to 300
In Table III solutions the component interrelationships are always such that the following holds:		
(12) mEq. ratio of bicarbonate$^-$/ CO_2	about 0.1/1 to 55/0.1	0.1 to 55/0.1
(13) mEq. ratio of l-lactate$^-$/ pyruvate$^-$	about 20/1 to 1/1	10/1 to 5/1
(14) mEq. ratio of d-betahydroxy-butyrate$^-$/ acetoacetate$^-$	about 6/1 to 0.5/1	3/1 to 1.5/1
(15) mEq. ratio of Na:Cl	about 1.24 to 1.60	1.24 to 1.6
(16) Osmolarity of Solution	about 260 to 5000	280 to 545
(17) pH of Solutions	about 5 to 9	5 to 9

*Glucose preferred

Optionally, solutions of this invention as shown in Table III can additionally contain:

(a) from 0 to about 25 millimoles per liter of sigma inorganic phosphate (e.g. all inorganic phosphate, including mono-, di-, and trivalent phosphate ions), and

(b) from 0 to about 2 millimoles per liter of sigma inorganic sulfate (e.g. all inorganic sulfate including non ionized dissolved salts).

The electrolyte solutions of such Table III, as indicated above, are useful in such applications as intravenous administration for replacement of electrolytes and fluids, for parenteral nutrition, for dialysis, and the like. For a particular field of use and/or end use applications, the formulation of any given solution can be optimized in accord with the desires of the formulator. Thus, in general, the present invention provides in one aspect an in vivo process which

(a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions,

(b) tends to maintain normal plasma and cellular pH, and

(c) tends to maintain normal cellular cofactor ratios (that is, tends to maintain and regulate a normal cellular redox state and a normal cellular phosphorylation potential).

This process is practiced by introducing into a living mammal a physiologically effective amount of an aqueous solution as above characterized. Introducing can be accomplished by any known procedure as herein indicated. The physiologically effective amounts are as herein indicated.

Class I solutions which are particularly suited for electrolyte and fluid therapy are subgenerically characterized in Table IV below. Each Table IV solution comprises water which has dissolved therein each of the indicated components in the respective amount indicated. In this Table IV the "preferred" class of embodiments (so identified) can be regarded as being usable either as such, or as concentrates which can be further diluted so long as nonionic material is included to keep the final osmolarity above about 260/mOsmoles/L. In the latter case, the diluted solutions should contain added dissolved nonionic material (preferably glucose) with care being taken to preserve in the product diluted solution the various ratios, osmolarity and pH values, all as shown in such Table IV.

Such Class I solutions are used, in accord with this invention, in an in vivo process for accomplishing electrolyte and fluid therapy in a mammal. This process:

(a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions,

(b) tends to maintain normal plasma and cellular pH, and

(c) tends to maintain normal cellular cofactor ratios.

This process comprises introducing intravenously into a mammal at a physiologically effective rate a quantity of such a solution in an amount which is not more than about 1 liter per 70 kilograms of mammal body weight per 24 hour day.

TABLE IV

Class I Solutions Particularly Suited for Electrolyte and Fluid Therapy

Component	Composition at time of Administration Quantity Range (millimoles per liter) broad	preferred
Total cations (mEq/L)	1 to about 2400	130 to 170
(1) sodium$^+$	1 to about 2400	130 to 165
(2) potassium$^+$	0 to about 90	0 to 10
(3) calcium^{++}	0 to about 60	0 to 5
(4) magnesium^{++}	0 to about 15	0 to 3
Total anions (mEq/L)	1 to about 2400	130 to 170
(5) chloride$^-$	0.6 to about 1935	80 to 130
(6) bicarbonate$^-$	0 to about 465	0 to 60
(7) sigma l-lactate/ plus pyruvate$^-$	0 to about 465	0 to 60
(8) sigma d-betahydroxy-butyrate$^-$ plus acetoacetate$^-$	0 to about 465	0 to 60
(9) sigma (6 + 7 + 8)	0.4 to about 465	25 to 60
Total nonionics	0 to about 2400	0 to 300
(10) carbon dioxide	0 to about 25	0 to 5
(11) osmotically active substances*	0 to about 2400	0 to 300
In Table IV solutions, the component interrelationships are		

TABLE IV-continued

Class I Solutions Particularly Suited for Electrolyte and Fluid Therapy

Component	Composition at time of Administration Quantity Range (millimoles per liter) broad	preferred
always such that:		
(12) mEq. ratio of HCO_3^-/ CO_2	about 0.1/1 to 55/0.1	12/1 to 85/1
(13) mEq. ratio of l-lactate$^-$/ pyruvate$^-$	about 20/1 to 1/1	10/1 to 5/1
(14) mEq. ratio of d-betahydroxy butyrate$^-$/ acetoacetate$^-$	about 6/1 to 0.5/1	3/1 to 1.5/1
(15) mEq. ratio of Na:CL	about 1.24 to 1.6	1.26 to 1.6
(16) Milliosmolarity of Solution	about 260 to 5000	260 to 540
(17) pH of Solution	about 5 to 9	7 to 8

*glucose preferred

Class II solutions which are particularly suited for electrolyte and fluid therapy are subgenerically characterized in Table V below. As before, each Table V solution comprises water which has dissolved therein the indicated components in the respective amount indicated. In this Table V, the "preferred" class of embodiments (so identified) can be regarded as being representative of compositions which are now believed to be suitable for usage for example by hospitals and the like. In making and using all these solutions care should be taken to preserve the various ratios, osmolarity, and pH values, all as shown in such Table V.

Such Class II solutions are used, in accord with this invention in an in vivo process for accomplishing electrolyte and fluid therapy in a mammal. Parenteral nutrition optionally can be concurrently accomplished (depending upon the content of nutrients, such as nonionic osmotically active substances (like glucose, or other conventional additives, including amino acids). As with the process involving Class I solutions, this process:

(a) tends to maintain the normal plasma milliequivalent ratio of sodium cations to chloride anions, and
(b) tends to maintain normal plasma and cellular pH ratios, and
(c) tends to maintain normal cofactor ratios.

This process comprises intravascularly introducing into the blood of a mammal a physiologically effective amount of such a solution. The quantity introduced can vary per 24 hour day per patient depending upon the circumstances, patient condition, physicians purpose, and the like. No minimum or maximum definite limit on safe usage quantity is now known or believed to exist.

TABLE V

Generic Composition of Class II Solutions For Electrolyte and Fluid Therapy

Component	Composition at time of Administration Quantity Range (millimoles per liter) broad	preferred
Total cations (mEq/L)	1 to about 170	136 to 170
(1) sodium$^+$	1 to about 170	130 to 160
(2) potassium$^+$	0 to about 10	3 to 5
(3) calcium^{++}	0 to about 5	1 to 1.5
(4) magnesium^{++}	0 to about 5	0.5 to 1.0
Total anions	1 to about 170	136 to 170

TABLE V-continued

Generic Composition of Class II Solutions For Electrolyte and Fluid Therapy

Component	Composition at time of Administration Quantity Range (millimoles per liter) broad	preferred
(5) chloride$^-$	0.6 to about 137	81 to 129
(6) bicarbonate$^-$	0 to about 64	0 to 51
(7) sigma l-lactate$^-$/ and pyruvate$^-$	0 to about 64	0 to 51
(8) sigma d-betahydroxy-butyrate$^-$/and acetoacetate$^-$	0 to about 64	0 to 51
(9) sigma (6 + 7 + 8)	0.4 to about 64	25 to 51
Total nonionics	about 0 to 625	0 to 305
(10) carbon dioxide	about 0 to 25	0 to 5
(11) osmotically active substances*	about 0 to 600	0 to 300
In Table V solutions the component interrelationships are always such that:		
(12) mEq. ratio of HCO_3^-/ CO_2	about 0.1/1 to 55/0.1	0.1/1 to 55/0.1
(13) mEq. ratio of l-lactate$^-$/ pyruvate$^-$	about 20/1 to 1/1	10/1 to 5/1
(14) mEq. ratio of d-betahydroxy-butyrate$^-$/ acetoacetate$^-$	about 6/1 to 0.5/1	3/1 to 1.5/1
(15) mEq. ratio of Na:Cl	about 1.24 to 1.6	1.24 to 1.6
(16) Milliosmolarity of Solution	about 260 to 950	260 to 550
(17) pH of Solution	about 5 to 9	5 to 9

*glucose preferred

Class II solutions which are particularly suited for use in dialysis (whether hemo- or peritoneal) are subgenerically characterized in Table VI below.

TABLE VI

Class II Solutions Particularly Suited for Dialysis (Hemo- & Peritoneal)

Component	Composition at Time of Administration Quantity Range (millimoles per liter) broad	preferred
Total cations (mEq/L)	about 130 to 170	136 to 155
(1) sodium$^+$	about 130 to 155	135 to 145
(2) potassium$^+$	0 to about 5	0 to 4
(3) calcium^{++}	0 to about 3	0 to 1.7
(4) magnesium^{++}	0 to about 2	0.3 to 1
Total anions (mEq/L)	about 130 to 170	136 to 155
(5) chloride$^-$	about 81 to 125	86 to 104
(6) bicarbonate$^-$	0 to about 60	25 to 45
(7) sigma l-lactate$^-$/plus pyruvate$^-$	0 to about 60	2 to 10
(8) sigma d-betahydroxy-butyrate$^-$/plus acetoacetate$^-$	0 to about 60	1 to 5
(9) sum (6 + 7 + 8)	about 25 to 60	27 to 55
Total nonionics	0 to about 525	11 to 280
(10) carbon dioxide	0 to about 25	0.5 to 2
(11) osmotically active substance*	0 to about 500	10 to 280
In Table VI Solutions, the component interrelationships are always such that:		
(12) mEq. ratio HCO_3^-/ CO_2	about 0.1/1 to 55/0.1	19/1 to 8/1
(13) mEq. ratio of L-lactate$^-$/ pyruvate$^-$	about 20/1 to 1/1	10/1 to 5/1
(14) meq/ratio of D-beta hydroxybutyrate$^-$/ acetoacetate$^-$	about 6/1 to 0.5/1	3/1 to 1.5/1

TABLE VI-continued

Class II Solutions Particularly Suited for Dialysis (Hemo- & Peritoneal)

Component	Composition at Time of Administration Quantity Range (millimoles per liter) broad	preferred
(15) mEq. ratio of Na:Cl	about 1.24 to 1.6	1.36 to 1.5
(16) Milliosmolarity of Solution	about 260 to 850	280 to 320
(17) pH of Solutions	about 5 to 9	7.35 to 8

*glucose preferred

Clase II solutions which are within the scope of Table VI above and which are particularly suited for hemodialysis are subgenerically characterized in Table VII below. As before, each Table VII solution comprises water which as dissolved therein the indicated components in the respective amounts indicated.

Such Class II solutions of Table VII are suitable for use in a hemodialysis process of the generally known and conventional type where renal function of a living mammal is replaced in whole or in part by dialysis. In hemodialysis, portions of the blood of such mammal are continuousy passed over one face of a dialysis membrane (which is incorporated preferably a high surface area cartridge-like structure) while the opposed face of such membrane is contacted with a dialysis fluid, thereby to achieve a change in the chemical composition of the body fluids after the so dialyzed blood is returned to the mammal's vascular system. Duration of a conventional hemodialysis can vary, depending upon equipment, conditions, patient condition, and the like, but typically can extend for a time of from about 3 to 5 hours. Optionally, but preferably, the dialysis membrane used in combination with the associated apparatus is such that the blood so passed over such membrane can be pressurized during such passage (typically and conventionally up to about 300 grams per cubic centimeter), thereby to produce what is known in the dialysis art as "ultrafiltration". In the conventional hemodialysis procedure, the dialysis fluid is an aqueous solution which contains dissolved therein the same principal inorganic electrolytes at respective individual concentration levels which approximate such major plasma electrolytes and their concentrations.

In the present hemodialysis one substitutes for the conventional dialysis fluid a solution of the present invention as above characterized in Table VII. Conventional dialysis equipment can be used, but a deaerator, such as might tend to eliminate dissolved carbon dioxide from a dialysis solution of this invention, should not be present. During use in peritoneal dialysis, a solution of this invention:

(a) tends to maintain a normal equivalent ratio of sodium cations to chloride anions, and

(b) tends to maintain normal cellular and plasma pH, and

(c) tends to maintain normal cofactor ratios.

The total quantity of such solution of this invention used in a given hemodialysis is comparable to the quantities used in prior art fluids employed under the same conditions (typically from about 35 to 160 liters of dialysis fluid per hemodialysis per man).

TABLE VII

Class II Solutions Particularly Suited for Hemodialysis

Component	Composition at Time of Administration Quantity Range (millimoles per liter) broad	preferred
Total cations (mEq/L)	about 130 to 170	134 to 154
(1) sodium$^+$	about 130 to 155	132 to 145
(2) potassium$^+$	0 to about 5	0 to 4
(3) calcium^{++}	0 to about 3	1 to 1.75
(4) magnesium^{++}	0 to about 2	0.3 to 0.75
Total anions (mEq/L)	about 130 to 170	134 to 154
(5) chloride$^-$	84 to about 125	93 to 115
(6) bicarbonate$^-$	0 to about 55	25 to 35
(7) sigma L-lactate$^-$/ pyruvate$^-$	0 to about 55	0 to 12
(8) sigma D-betahydroxy-butyrate$^-$/ acetoacetate$^-$	0 to about 55	0 to 5
(9) sigma (6 + 7 + 8)	about 25 to 55	36 to 42
Total nonionics*	about 0 to 525*	0 to 12
(10) carbon dioxide	about 0 to 25	0 to 2
(11) osmotically active substance**	about 0 to 500*	0 to 10
In Table VII, the component interrelationships are always such that:		
(12) mEq. ratio of bicarbonate$^-$/ CO_2	about 0.1/1 to 55/0.1	18/1 to 35/0.5
(13) mEq. ratio of L-lactate$^-$/ pyruvate$^-$	about 20/1 to 1/1	10/1 to 5/1
(14) mEq. ratio of D-beta-hydroxybutyrate$^-$/ acetoacetate$^-$	about 6/1 to 0.5/1	3/1 to 1.5/1
(15) mEq. ratio of Na:Cl	about 1.24 to 1.6	1.26 to 1.55
(16) milliosmolarity of Solution	about 260 to 800	260 to 350
(17) pH of Solution	about 5 to 9	7.35 to 8

*This upper limit used when the solution is being employed in an old type Kolff kidney where pressure cannot be exerted on the dialysis membrane. In a pressurized dialysis system the limit is about 0 to 11 mMol/l for glucose; if other nonionics are added, then preferred limit would be below about 20 mMol/l total.

**glucose preferred

Class II solutions which are within this scope of Table VI above and which are particularly suited for peritoneal dialysis are subgenerically characterized in Table VIII below.

Such Class II solutions of Table VIII are suitable for use in a peritoneal dialysis process of the generally known and conventional types when renal function of a living mammal is replaced in whole or in part by dialysis. In peritoneal dialysis a quantity of a dialysis fluid is charged into the peritoneal cavity of such mammal for a time sufficient to achieve a change in the chemical composition of body fluids, after which the dialysate is drained or otherwise removed from the peritoneal cavity. Typical residence times for fluid in the peritoneal cavity range from about ½ to 1 hour, although longer and shorter times can be employed. Typically, peritoneal dialysis sessions last 4½ hours, but continuous ambulatory peritoneal dialysis has recently been advocated. The patient's own peritoneum serves as a dialysis membrane. In the conventional peritoneal dialysis procedure, the dialysis fluid is, as in the case of a hemodialysis fluid, an aqueous solution which contains dissolved therein the same principal inorganic electrolytes and at respective individual concentration levels which approximate those of major plasma electrolytes and their concentrations, except that in the case of peritoneal dialysis fluids a higher concentration of nonionics, such

as glucose, is typically employed in order to provide as osmolarity which is greater than that of mammalian plasma, thereby to promote ion and water transfer through the peritoneum, all as known to those skilled in the art. Chronic, so called "ambulatory" peritoneal dialysis may also benefit from these solutions.

In the present invention, one substitutes for the conventional dialysis fluid a solution of the present invention as above characterized in Table VIII. During use in peritoneal dialysis, a solution of this invention:

(a) tends to maintain a normal equivalent ratio of sodium cations to chloride anions,

(b) tends to maintain normal plasma and cellular pH,

(c) tends to maintain normal cofactor ratios.

The quantity of such solution employed is comparable to the quantity used in prior art peritoneal dialysis as is the residence time in the peritoneal cavity.

TABLE VIII

Class II Solutions Particularly Suited for Peritoneal Dialysis

Component	Compositions at Time of Administration Quantity Range (millimoles per liter) broad	preferred
Total cations	about 130 to 170	135 to 150
(1) sodium$^+$	about 130 to 165	130 to 145
(2) potassium$^+$	about 0 to 5	0 to 4
(3) calcium^{++}	about 0 to 2	1 to 1.5
(4) magnesium^{++}	about 0 to 1.5	0.3 to 1
Total anions	about 130 to 170	135 to 150
(5) chloride$^-$	about 81 to 130	93 to 102
(6) bicarbonate$^-$	about 0 to 55	25 to 30
(7) sigma L-lactate$^-$/plus pyruvate$^-$	about 0 to 55	2 to 12
(8) sigma D-betahydroxybutyrate$^-$/acetoacetate$^-$	about 0 to 55	1 to 5
(9) sigma (6 + 7 + 8)	about 26 to 55	36 to 50
Total nonionics*	about 40 to 252	84 to 238
(10) carbon dioxide	about 0 to 25	0 to 2
(11) osmotically active substance	about 40 to 250	83 to 237
In Table VIII, the component interrelationships are always such that:		
(12) mEq. ratio of HCO_3^-/CO_2	about 0.1/1 to 160/1	19/1 to 21/1
(13) mEq. ratio of L-lactate$^-$/pyruvate$^-$	about 20/1 to 1/1	10/1 to 5/1

TABLE VIII-continued

Class II Solutions Particularly Suited for Peritoneal Dialysis

Component	Compositions at Time of Administration Quantity Range (millimoles per liter) broad	preferred
(14) mEq. ratio of D-beta-hydroxybutyrate$^-$/acetoacetate$^-$	about 6/1 to 0.5/1	3/1 to 1.5/1
(15) mEq. ratio of Na:Cl	about 1.24 to 1.6	1.36–1.42
(16) Milliosmolarity of Solution	about 310 to 615	350 to 520
(17) pH of Solution	about 5 to 8	7.36 to 7.6

*glucose preferred

EMBODIMENTS

The following examples are merely illustrative of the present invention and are not intended as a limitation upon the scope thereof.

EXAMPLES 1 THROUGH 27

The following compositions of this invention illustrate electrolyte solutions of Class I (above identified) which are suitable for intravenous administration to replace electrolytes and fluid in a human adult patient at dose rates of, for example, 500 ml/patient/24 hour day. Each solution consists of water which has dissolved therein each of the identified in the respective specific per liter quantity shown components in the following Table IX.

Each solution is here prepared by dissolving substantially pure selected salt and nonionic material following the teaching of "Date for Biochemical Research", 1969, pp. 507–508. Each solution can be made from many different materials depending upon manufacturing convenience, ease of sterilization, cost of raw materials, and the like; the only requirement is that the final ionic composition of each solution should be as described.

The footnote for each example in Table IX characterizes the composition and provides a suggested application or use.

Also shown in Table IX are further examples of prior art solutions. All solutions are listed as Type 1 a, b, c, and d, in conformity with the classification herein developed.

TABLE IX

Case 1

Class Ia

Solutions Containing 1 or 2 Cations from Among Na^+, K^+, Mg^{2+} or Ca^{2+} with no Nutrients (Glucose) and No HCO_3^-/ CO_2

	Normal Plasma	Ia1 "Normal"	Ia2 "Normal"	Ia3 Isotonic	1 Ia4 Isotonic	2 Ia5 Isotonic	3 Ia6 Isotonic
Units	N.E.J.M.	0.9% NaCl	0.95% NaCl	NaLactate	NaLact/Pyr	NaLact/Pyr-	Na BHB/acac
mmoles	283, 1285	U.S.	U.K.	Salt	Salt	BHB/acac	Salt
L fluid	1970						
Na	136–145	155	162.5	160.3	153	155	152.5
K	3.5–5.0						2.5
Ca	2.1–2.6				1		
free $[Ca^{2+}]$	[1.06]						
Mg	0.75–1.25						
free $[Mg^{2+}]$	[0.53]						

TABLE IX-continued

Case 1

Σ mEq Cations	142.7–153.2	155	162.5	160.3	155	155	155
Cl	100–106	155	162.5	108.3	106	106	106
HCO_3	26–28						
ΣPi	1–1.45						
SO_4	0.32–0.94						
L - lactate	0.6–1.8			52 (d,l)	44	38	
pyruvate					5	5	
Lact/pyr				oo	8.8	9.5	
D B OHbutyrate						4.7	35
acetoacetate						2.3	14
B HB/acac						2.0	2.5
acetate							
Other							
Σ mEq anions	128.7–139.4	155	162.5	160.3	155	155	155
Na/Cl	1.28–1.45	1.00	1.00	1.48	1.44	1.46	1.44
Glucose	3.9–5.6						
or others							
CO_2	0.99–1.39						
pH	7.35–7.45	~5.5–6.5	~5.5–6.5	~6.5	~6.5	~6.5	~6.5
Σ mOsm	285–295	310	325	321	310	310	310
Use:		I.V. electrolyte replacement	same as Ia1	Used to prevent acidosis	Improves Ia1, Ia2 Ia3 with Ca^{2+}	Redox control of cytoplasm & mitochondria	Alternative to Ia4 with K

Ia.1. Most common electrolyte solution given in U.S. Tends of cause hyperchloremic acidosis because of adnormal Na/Cl ratio. See Black DAK. Lancet i, 353, 1952.
Ia.2. Used in U.K. and Canada.
Ia.3. Darrow et al. J Am Med Ass 143: 365, 432, 1944. Causes redox imbalance.
Ia.4. | |- Solutions in boxes are new in this disclosure.

Class Ib

Solutions Containing 1 or 2 Cations from Among Na^+, K^+, Mg^{2+}, Ca^{2+} with HCO_3^- or HCO_3^-/CO_2 and No Nutrients

Units mmoles L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	Ib 1 Isotonic $NaHCO_3^-$ Salt	4 Ib 2 Isotonic $NaHCO_3/CO_2$+ Lact/Pyr	5 Ib 3 Isotonic NaLact/pyr+ NaCl + Ca	6 Ib 4 Isotonic NaL/P-B/A- HCO_3/CO_2	7 Ib 5 Ib 4 with K+
Na	136–145	160.3	155	153	155	152
K	3.5–5.0					3
Ca	2.1–2.6			1		
free $[Ca^{2+}]$	[1.06]					
Mg	0.75–1.25					
free $[Mg^{2+}]$	[0.53]					
Σ mEq Cations	142.7–153.2	160.3	155	155	155	155
Cl	100–106	108.3	106	106	106	106
HCO_3	26–28	52	27	27	27	27
ΣPi	1–1.45					
SO_4	0.32–0.94					
L - lactate	0.6–1.8		19	19	13	13
pyruvate			3	3	2	2
Lact/pyr			6.3	6.3	6.5	6.5
D B OHbutyrate					5	4
acetoacetate					2.5	3
B HB/acac					2.5	1.3
acetate						
Other						
Σ mEq anions	128.7–139.4	160.3	155	155	155	155
Na/Cl	1.28–1.45	1.48	1.46	1.44	1.46	1.43
Glucose	3.9–5.6					
or others						
CO_2	0.99–1.39	—	1.3	1.3	1.3	1.3
pH	7.35–7.45	8.6	7.35	7.35	7.35	7.35
Σ mOsm	285–295	321	311	311	311	311

TABLE IX-continued

Case 1

Use:

1 b 1 Darrow et al J Am Med Ass 143: 365, 432, 1944, abnormal pH. Incompatible with Mg^{2+} and Ca^{2+}.

Class 1c

Solutions Containing 1 or 2 Cations from Among Na^+, K^+, Mg^{2+} or Ca^{2+} with Non-Ionic Nutrients*

Units mmoles L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	1 c 1 5% Dextrose + H_2O U.S.	1 c 2 5.25% Glucose U.K.	1 c 3 Isotonic Glucose 2+ NaCl 1	1 c 4 Glucose NaLactate-NaCl	8 1 c 5 Glucose NaLact/Pyr-NaCl	9 1 c 6 Glucose + Ketones + NaCl	10 1 c 7 Redox Balanced 2 Gluc + 1 NaCl
Na	136–145			54.1	53.4	53.4	52.4	53.4
K	3.5–5.0							
Ca	2.1–2.6							
free $[Ca^{2+}]$	[1.06]							
Mg	0.75–1.25						0.5	
free $[Mg^{2+}]$	[0.53]							
mEq Cations	142.7–153.2	0	0	54.1	53.4	53.4	53.4	53.4
Cl	100–106			54.1	36.1	36.1	36.1	36.1
HCO_3	26–28							
Pi	1–1.45							
SO_4	0.32–0.94							
L - lactate	0.6–1.8				1.73 (d,l)	15.3		10
pyruvate						2		2
Lact/pyr					oo	7.7		5
D B OHbutyrate							12	3.3
acetoacetate							5.3	2
B HB/acac							2.3	1.65
acetate								
Other								
mEq anions	128.7–139.4	0	0	54.1	53.4	53.4	53.4	53.4
Na/Cl	1.28–1.45	—	—	1.00	1.48	1.48	1.45	1.48
Glucose	3.9–5.6	278	292	195	195	195	195	195
or others								
CO_2	0.99–1.39							
pH	7.35–7.45	~6.5	~6.5	~6.5	~6.5	~6.5	~6.5	~6.5
mOsm	285–295	278	292	301	302	302	302	302
Use:		fluid replacement + nutrients	same as 1 c 2	NaCl, H_2O replacement + calories	Prevent hyperchlor-emia	Corrects redox imbal-ance in 1 c 4	Alternative also for status epilepticus	Improves 1 c 5

*Common non-ionic nutrients are 5%, 2.5%, 10% glucose. Additional similar fructose and glycerol solutions in over 20 mM amounts are approved by FDA, but not recommended here. (See "Safe Entry Points")

1 c 1 - Most common I.V. fluid given. Merck Handbook 1966, p 1867. This is combined with isotonic NaCl in many proportions.

1 c 2 - Used in the U.K. and Canada where "isotonic" is different than in the U.S. - presumably. See Geigy Handbook, 1970, p 334.

1 c 3 - 2 parts isotonic glucose plus 1 part isotonic NaCl - Geigy Handbook 1970, p 334.

1 c 4 - Prevents hyperchloremia but causes redox imbalance. Geigy Handbook 1970, p 334.

Units mmoles L fluids	Normal Plasma N.E.J.M. 283, 1285 1970	11 1 c 8 2L D5W + 0.5L Normal Saline + Redox Balance	12 1 c 9 11 with K	1 c 10 D 5 W + 0.9% NaCl	1 c 11 10% Glucose + 0.9% NaCl	1 c 12 2.5% Glucose + 0.45% NaCl	13 1 c 13 D5W + L/P Saline	14 1 c 14 D10W + BHB/Acac + Saline	15 1 c 15 D5W + Redox Balance
Na	136–145	31	31	154	154	77	154	154	154
K	3.5–5.0		5.0						
Ca	2.1–2.6								
free $[Ca^{2+}]$	[1.06]								
Mg	0.75–1.25								
free $Mg^{2+}]$	[0.53]								

TABLE IX-continued

Case 1

Σ mEq Cations	142.7–153.2	31	36	154	154	77	154	154	154
Cl	100–106	22	22	154	154	77	105	105	105
HCO_3	26–28								
ΣPi	1–1.45								
SO_4	0.32–0.94								
L - lactate	0.6–1.8	7	10				43		36
pyruvate		1	1.43				6		6
Lact/pyr		7	7				7.2		7
D B OHbutyrate		0.66	1.57					29	4
acetoacetate		0.33	1.00					20	3
B HB/acac		2	1.6					1.5	1.3
acetate									
Other									
Σ mEq anions	128.7–139.4	31	36	154	154	77	154	154	154
Na/Cl	1.28–1.45	1.41	1.41	1.00	1.00	1.00	1.47	1.47	1.47
Glucose	3.9–5.6	222.4	222.4	278	556	139	278	556	278
or others									
CO_2	0.99–1.39								
pH	7.35–7.45	~6.5	~6.5	~5.5–6.5	~5.5–6.5	~5.5–6.5	~5.5–6.5	~5.5–6.5	~5.5–6.5
Σ mOsm	285–295	284	284	561	813	293	561	864	561
Use:							Improves l c 10 with Redox & Na/Cl Balance	Improves l c 11	Improves l c 13

l c 8. Improves with normal Na/Cl ratio and redox balance the most common routine I.V. order in the U.S.

l c 9. Replaces 12.5 mEq of the 40 mEq of K^+ lost/day when given at the usual rate of 2.5L/day.

l c 10. Facts and Comparisons Oct. 81, p. 51, Lippincott, St Louis

l c 11. Facts and Comparisons Oct. 81, p. 51, Lippincott, St Louis

l c 12. Facts and Comparisons Oct. 81, p. 51, Lippincott, St Louis

Class 1d

Solutions Containing 1 or 2 Cations from Among Na^+, K^+, Mg^{2+}, or Ca^{2+} plus Non-ionic Nutrients Plus HCO_3^-/CO_2

Units mmoles L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	16 1 d 1 HCO_3^-/CO_2 Saline	17 1 d 2 HCO_3^-/CO_2 Saline + K	18 1 d 3 HCO_3^-/CO_2 Saline + Mg	19 1 d 4 HCO_3^-/CO_2 Saline + Ca	20 1 d 5 L/P HCO_3/CO_2 Saline	21 1 d 6 L/P HCO_3/CO_2 Saline + K	22 1 d 7 Redox Bal. Saline HCO_3 + 5% Gluc.	23 1 d 8 Redox Bal. Saline HCO_3 + 2.5% Gluc
Na	136–145	155	155	155	155	145	145	141	140
K	3.5–5.0		5				4		4
Ca	2.1–2.6								
free $[Ca^{2+}]$	[1.06]				1.5				
Mg	0.75–1.25			1.0					
free $[Mg^{2+}]$	[0.53]								
Σ mEq Cations	142.7–153.2	155	160	156	158	145	149	141	144
Cl	100–106	107	107	107	107	106	106	100	104
HCO_3	26–28	48	53	49	51	29	29	29	29
ΣPi	1–1.45								
SO_4	0.32–0.94								
L - lactate	0.6–1.8					8.8	12.5	7	7
pyruvate						1.2	1.5	1	1
Lact/pyr						7.3	8	7	7
D B OHbutyrate								2	2
acetoacetate								1	1
B HB/acac								2	2
acetate									
Other									

TABLE IX-continued

		Case 1							
Σ mEq anions	128.7-139.4	155	160	156	158	145	149	141	144
Na/Cl	1.28-1.45	1.45	1.45	1.45	1.45	1.37	1.37	1.41	1.35
Glucose or others	3.9-5.6	10 (optional)	10	10	10	10	10	278	139
CO_2	0.99-1.39	2.7	2.75	2.71	2.74	1.45	1.45	1.45	1.45
pH	7.35-7.45	7.35	7.35	7.35	7.35	7.4	7.4	7.4	7.4
Σ mOsm	285-295	320	330	322	328	290	298	560	427
Use:		Improves normal NaCl leaves patient alkolotic	Replaces K loss	Mg^{2+} does not precipitate	Ca^{2+} does not ppt. as with HCO_3^- alone.				

Class Id
Solutions Containing 1 or 2 Cations, to which is added HCO_3^-/CO_2 and Non-ionic Nutrients

Units mmole L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	24 1 d 9 2L D5W + 0.5L R.B. Saline	25 1 d 10 2L D5W + 0.5L R.B. Saline + K	26 1 d 11 R.B. Saline with K & 2.5% Gluc. & No added CO_2	27 1 d 12 Like 1d11 but BHB acid added to make CO_2 in situ
Na	136-145	28.2	28.2	140	140
K	3.5-5.0		5	4	4
Ca	2.1-2.6				
free $[Ca^{2+}]$	[1.06]				
Mg	0.75-1.25				
free $[Mg^{2+}]$	[0.53]				
Σ mEq Cations	142.7-153.2	28.2	33.2	144	144
Cl	100-106	20	20	104	104
HCO_3	26-28	5.8	10.8	29	29
ΣPi	1-1.45				
SO_4	0.32-0.94				
L - lactate	0.6-1.8	1.4	1.4	5	7
pyruvate		0.2	0.2	1	1
Lact/pyr		7	7	*7	7
D B OHbutyrate		0.4	0.4	2	*
acetoacetate		0.2	0.2	1	1
B HB/acac		2	2	2	2
acetate					
Other				*2 Hlactate	*2 d B hydroxybutyric acid
Σ mEq anions	128.7-139.4	28.2	33.2	144	144
Na/Cl	1.28-1.45	1.41	1.41	1.35	1.35
Glucose or others	3.9-5.6	222.4	222.4	139	139
CO_2	0.99-1.39	0.29	0.54	*—	*—
pH	7.35-7.45	7.4	7.4	~7.4	~7.4
Σ mOsm	285-295	279	289	427	427
Use:		Replaces 2l D5W & 0.5l Normal Saline	& Replaces K loss		

1 d 11 *L Lactic acid is added instead of CO_2 to generate CO_2 in situ.
1 d 12 *D B Hydroxybutryric acid is added to generate CO_2 in situ.

EXAMPLES 28 THROUGH 41

The following compositions of this invention illustrate electrolyte solutions of Class II (above identified) which are suitable for (a) intravenous use to replace electrolytes and fluid (b) providing parenteral nutrition in a human adult patient, (c) peritoneal dialysis, and (d) hemodialysis. Dose rates can vary. Each solution consists of water which has dissolved therein each of the identified components in the respective specified concentrations per liter quantity shown in the following Table X. Each solution is prepared by conventional procedures. (See text of Examples 1 through 27).

The footnote for each sample in Table X characterizes the composition and provides a suggested application or use.

These compositions demonstrate, as do Tables V through VIII (above), that there is no essential compositional difference between these various solutions.

Table XI shows prior art hemodialysis fluids for comparison purposes in dialyzing a human adult patient using, for example, an apparatus as described by Miller J. H., Schinaberger J. H., Kraut J. A., and Gardner P. S., *Trans. Am. Soc. Artif. Intern. Organs* 25, 404–408, 1979.

In these solutions which contain dissolved CO_2, no deaerator should be used on the dialysis equipment.

TABLE X

Class 2a Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contacting Cells, Containing No HCO_3^-/CO_2 and No Glucose: eg. after S. J. Ringer, Physiol 4: 29, 223, 1883, and 7: 291, 1886.

Units mmoles L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	2. a. 1. Ringer's Injection U.S.	2. a. 2. Lactated Ringer's	2. a. 3. Lactated Ringer's (Commercial)	2. a. 4. Acetated Ringer's U.S.	2. a. 5. Lact/Acet Ringer's	28 2. a. 6. Lact/Pyr Ringer's	29 2. a. 7. dB-HB/acac Ringer's	30 2. a. 8. Redox Balanced Ringer's
Na	136–145 *(137–145)	147	129.8	130	130	140	130	130	130
K	3.5–5.0	4	5.4	4	4	10	4	4	4
Ca	2.1–2.6	2.5	0.9	1.5	1.5	2.5	1.5	1.5	1.5
free [Ca2+]	[1.06]								
Mg	0.75–1.25		1.0			1.5			
free [Mg2+]	[0.53]								
ΣmEq Cations	142.7–153.2	156	139	137	137	158	137	137	137
Cl	100–106 *(100–110)	156	111.8	109	109	103	96	96	96
HCO_3	26–28								
ΣPi	1–1.45								
SO_4	0.32–0.94								
L-lactate	0.6–1.8		27.2 (d,l)	28 (d,l)		27.5 (d,l)	35.9		30
pyruvate							5.1		4
Lact/pyr			oo	oo		oo	7		7.5
D B OHbutyrate								27.3	5
acetoacetate								13.7	2
B HB/acac								2	2.5
acetate					28	27.5			
Other									
ΣmEq anions	128.7–139.4	156	139	137	137	158	137	137	137
Na/Cl	1.28–1.45 *(1.245–1.45)	0.94	1.16	1.19	1.19	1.36	1.35	1.35	1.35
Glucose or others	3.9–5.6								
CO_2	0.99–1.39								
pH	7.35–7.45								
ΣmOsm	285–295	309	276	272	272	312	272.5	272.5	272.5
Use:		I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	Improves 2 a 3.	Improves 2 a 4	Improves 2 a 3, 2 a 6, 2 a 7.

*N.I.H. Path & Blood Bank Guide, Revised Nov 1, '82.

2. a. 1. Facts and Comparisons p50, Oct '81, Lippincott

2. a. 2. Hartmann A F. J. Am. Med. Ass. 103: 1349, 1934.

2. a. 3. Facts and Comparisons p50, Oct '81, Lippincott. Widely used in blood product administration and surgery

2. a. 4. Facts and Comparisons p50, Oct '81, Lippincott.

2. a. 5. Fox et al. J. Am. Med. Ass. 148: 827, 1952. Corrects abnormal Na/Cl ratio but by use of pathogenic organic anions.

Solutions with Bold numbers and in boxes are new disclosures.

Units mmoles L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	31 2 a 9 Redox Balanced Ringer's & High K	2 a 10 Ionosol D-CM (Abbott)	2 a 11 Plasmalyte (Travenol)	2 a 12 Isolyte S (McGaw) PolyonicR148 (Cutter)	2 a 13 Isolyte E (McGaw)	2 a 14 Delbecco's Pi Buffered Saline	2 a 15 Krebs Ringer Phosphate
Na	136–145	140	138	140	140	140	152	150.76
K	3.5–5.0	10	12	10	5	10	4.17	5.92
Ca	2.1–2.6	1.0	2.5	2.5		2.5	0.9	2.54
free [Ca2+]	[1.06]							

TABLE X-continued

Mg free [Mg2+]	0.75–1.25 [0.53]	0.5	1.5	1.5	1.5	1.5	0.45	1.18
ΣmEq Cations Cl	142.7–153.2 100–106	153 103	158 108	158 103	148 98	158 103	159.15 140.5	164.12 131.51
HCO_3 ΣPi SO_4	26–28 1–1.45 0.32–0.94						9.8 0.45	17.38 1.18
L-lactate pyruvate Lact/pyr	0.6–1.8	38 5 7.6	50 (d,l) oo	8 (d,l) oo				
D B OHbutyrate acetoacetate B HB/acac		5 2 2.5						
acetate Other			47	27 23 gluconate	49 4 citrate			
ΣmEq anions Na/Cl	128.7–139.4 1.28–1.45	153 1.36	158 1.28	158 1.36	148 1.43	158 1.40	159.18 1.08	163.97 1.15
Glucose or others CO_2 pH	3.9–5.6 0.99–1.39 7.35–7.45						 7.4	 7.4
ΣmOsm	285–295	304.5	312	312	294	315	308.3	311.65
Use:		Improves 2 a 5, lowers Ca & Mg to normal	I.V. electrolyte therapy	Same as 2 a 10 redox imbalance	Same as 2 a 10 PPi accumulation	Same as 2 a 10 imbalance of NADP/NADPH	Tissue culture salt mix	Biochemical experiments

2 a 10. Facts and Comparisons Oct '81, p50
2 a 11. Facts and Comparisons Oct '81, p50
2 a 12. Facts and Comparisons Oct '81, p50
2 a 13. Facts and Comparisons Oct '81, p50
2 a 14. Delbecco R, Vogt M. J Exp Med 99: 167–182, 1954
2 a 15. Krebs H A. Hoppe-Seyle's Z Physiol Chem 217: 193, 1933

Class 2b Electrolyte Fluids Containing 3 to 4 Cations Suitable for Contacting Cells Also Containing HCO_3^-/CO_2 and No Glucose after Krebs H A & Henseleit K A. Hoppe-Seyler's Z Physiol Chem 210: 33–66, 1932.

Units mmoles L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	2 b 1 Krebs Henseleit	32 2 b 2 Redox Balanced Ringer's HCO_3/CO_2	33 2 b 3 Redox Balanced Ringer's & HCO_3/CO_2 & Mg	34 2 b 4 High HCO_3 Ringer sine Redox Balance	35 2 b 5 L/P Ringer's Lactate HCO_3/CO_2	36 2 b 6 Ringer's Ketones HCO_3/CO_2
Na K	136–145 3.5–5.0	143 5.9	130 4	136 4	136 4	130 4	130 4
Ca free [Ca2+]	2.1–2.6 [1.06]	2.5	1.5	1	1	1.5	1.5
Mg free [Mg2+]	0.75–1.25 [0.53]	1.2		0.5	0.5		
ΣmEq Cations Cl HCO_3	142.7–153.2 100–106 26–28	156.3 127.8 25	137 96 29	143 100 29	143 100 43	137 96 29	137 96 29
ΣPi SO_4	1–1.45 0.32–0.94	1.18 1.2					
L-lactate pyruvate Lact/pyr	0.6–1.8		7 1 7	9 1 9		10.5 1.5 7	
D B OHbutyrate acetoacetate B HB/acac			3 1 3	3 1 3			8 4 2
acetate Other							

TABLE X-continued

ΣmEq anions	128.7-139.4	157.3	137	143	143	137	137
Na/Cl	1.28-1.45	1.12	1.35	1.36	1.36	1.35	1.35
Glucose or others	3.9-5.6						
CO_2	0.99-1.39	1.24	1.5	1.5	2.46	1.5	1.5
pH	7.35-7.45		7.4	7.4	7.4	7.4	7.4
ΣmOSm	285-295	308	274	286	286	274	274
Use:		Tissue incubation, organ perfusion	To replace all previous Lactated Ringer's	For blood replace-ment	For Rx of acidosis	Alternate to 2 b 2	Alternate to 2 b 5

2 b 2 to 2 b 6. All these solutions would be suitable, given added glucose, for peritoneal dialysis, ie like class 2 c. As it is, these solutions would improve existing hemodialysis.

Class 2c Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contacting Cells Containing No HCO_3^-/CO_2 to which are Added Non-ionic nutrients such as Glucose, Fructose, Glycerol etc.

Units mmoles	Normal Plasma N.E.J.M. 283,1285	2 c 1 Lactated Ringer's 5% Glucose	2 c 2 ½ Strength Lactated Ring + 2.5% Gl	2 c 3 Acetated Ringers & 5% 5% Glucose	2 c 4 Ionosol B & 5% Glucose (Abbott)	2 c 5 Dianeal & 1.5% Glucose (Travenol)	2 c 6 Peritoneal Dialysis 4.25% Gluc (Am. McGaw)	2 c 7 Dianeal K-141 & 4.25% Glucose (Travenol)
L fluid	1970							
Na	136-145	130	65	130	57	141	141.5	132
K	3.5-5.0	4	2	4	25			4
Ca	2.1-2.6	1.5	0.75	1.5		1.75	2.0	1.875
free [Ca2+]	[1.06]							
Mg	0.75-1.25				2.5	0.75	0.75	0.75
free [Mg2+]	[0.53]							
ΣmEq Cations	142.7-153.2	137	68.5	137	87	146	147	141
Cl	100-106	109	55	109	49	101	102.5	106
HCO_3	26-28							
ΣPi	1-1.45				6.5 $H_2PO_4^-$			
SO_4	0.32-0.94							
L-lactate pyruvate	0.6-1.8	28 (d,l)	14 (d,l)		25 (d,l)	45 (d,l)		35 (d,l)
Lact/pyr		oo	oo		oo	oo		oo
D B OHbutyrate acetoacetate								
B HB/acac								
acetate				28			44.5	
Other								
ΣmEq anions	128.7-139.4	137	69	137	87	146	147	141
Na/Cl	1.28-1.45	1.19	1.18	1.19	1.16	1.40	1.38	1.25
Glucose or others	3.9-5.6	278	139	278	278	83	236	236
CO_2	0.99-1.39							
pH	7.35					~5.5-6.5	~5.5-6.5	~5.5-6.5
ΣmOsm	285-295	524? *(550.5)	263	523	443	366	510	494
Use:		I.V. therapy for dehydration	I.V. therapy same as 2 c 1	I.V. therapy same as 2 c 1	Parenteral nutrition	Peritoneal dialysis	Peritoneal dialysis	Peritoneal dialysis

*2 c 1. Facts and Comparisons Oct '81, p 52. The osmolarity listed by the reference appears to be incorrect at 524 mOsm. The correct osmolarity appears to be 550.5 mOsm.

2 c 2-2 c 3. Facts and Comparisons Oct '81, p52. Lippincott, St Louis

2 c 4. Facts and Comparisons Oct '81, p52. Lippincott, St Louis

2 c 5-2 c 7. Facts and Comparisons Oct '82, p704, Lippincott, St Louis

Units mmoles L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	37 2 c 8 L/P, BHB/Acac Ringer's & 5% Gluc	38 2 c 9 Na/Cl, L/P Balanced Ringer's & 5% Gluc
Na	136-145	130	130
K	3.5-5.0	4	4
Ca	2.1-2.6	1.5	1.5
free [Ca2+]	[1.06]		
Mg	0.75-1.25		
free [Mg2+]	[0.53]		
ΣmEq Cations	142.7-153.2	137	137
Cl	100-106	104	96
HCO_3	26-28		
ΣPi	1-1.45		

TABLE X-continued

SO_4	0.32-0.94			
L-lactate	0.6-1.8	24.5	35.9	
pyruvate		3.5	5.1	
Lact/pyr		7	7	
D B OHbutyrate		3		
acetoacetate		2		
B HB/acac		1.5		
acetate				
Other				
ΣmEq anions	128.7-139.4	137	137	
Na/Cl	1.28-1.45	1.24	1.35	
Glucose	3.9-5.6	278	278	
or others				
CO_2	0.99-1.39			
pH	7.35-7.45			
ΣmOsm	285-295	550.5	550.5	
Use:		Improved 2 c l. with redox balance and normal Na/Cl	2 a 6 with Gluc. Normal BHB/Acac normal Na/Cl ratio	

Class 2d Electrolyte Fluids for Contacting Living Cells Containing 3 to 4 Cations plus Non-Ionic Nutrients plus HCO_3^-/CO_2.

Units mmoles / L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	2 d 1 Krebs Serum Substitute	2 d 2 Tyrode's Solution	39 2 d 3 Veech's Redox Balanced Salt Solution	40 2 d 4 Veech's R.B.-Salt sine Pi cum 5% Glucose	41 2 d 5 Veech's R.B.-Salt sine Pi
Na	136-145	141	151.54	142	140.4	141
K	3.5-5.0	5.93	5.9	4.5	4.5	4
Ca	2.1-2.6	2.54	1.8	1.1	1.1	1.1
free [Ca2+]	[1.06]			[1.06]		
Mg	0.75-1.25	1.18	0.45	0.56	0.56	0.56
free [Mg2+]	[0.53]			[0.53]		
ΣmEq Cations	142.7-153.2	154.37	162.07	149.82	148.2	148.3
Cl	100-106	104.8	147.8	102	102	102
HCO_3	26-28	24.9	11.9	29	29	29
ΣPi	1-1.45	1.23	1.22#	1.1*		
SO_4	0.32-0.94	2.36		[0.7]		
L-lactate	0.6-1.8		1.33	10.7	10.7	10.8
pyruvate		4.9	0.09	1.5	1.5	1.5
Lact/pyr			14.8	7	7	7
D B OHbutyrate				3	3	3
acetoacetate				2	2	2
B HB/acac				1.5	1.5	1.5
acetate						
Other		2.45 glutamate$^-$ 5.4 fumerate^{2-}				
ΣmEq anions	128.7-139.4	154.47	162.81	149.82	148.2	148.3
Na/Cl	1.28-1.45	1.35	1.03	1.39	1.38	1.38
Glucose	3.9-5.6	9.2	5.45	10	277	10
or others						
CO_2	0.99-1.39	1.0	1.17	1.45	1.45	1.45
pH	7.35-7.45	7.4	7.1	7.40	7.40	7.40
ΣmOsm	285-295	308.2	328	308.6	573.2	306.4

TABLE X-continued

Use:	Media tissue slices	For liver perfusion	For I.V. or general use to replace 2 b 1 & 2 d 1	for peritoneal dial. or I.V.	for I.V. & peritoneal dialysis

2 d 1. Krebs H A. Biochem Biophys Acta 4: 249-269, 1950
2 d 2. Tyrode M. J. Arch int Pharmacodyn 20: 205. 1910. # For use in liver perfusion with albumin see Schimassek H. Biochem Z 336: 460, 1963
2 d 3. *The apparent charge on sum Pi in the presence of these cations is about 1.46 not 1.8 presumably due to cation binding.

TABLE XI

Prior Art Hemodialysis Fluids. For recent discussion see Parsons FM, Stewart WK. Composition of Dialysis Fluid. In: Replacement of Renal Function by Dialysis (Drucker W, Parsons Fm, Maher JP, eds.) Martinus Nijhoff, Hingham, pp 148-170, 1983.

Units mmoles / L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	2 d 6 Kolff 1947	2 d 7 Brigham 1952	2 a 16 Scribner's Acetate 1964	2 a 17 Commercial Acetate 1981	2 a 18 Bjaelder "Low" Acet. 1981	2 a 19 Kraut "High" Acet. 1981	2 b 2 COBE HCO_3—Acetic Acid, 1981	2 b 3 HCO_3—Acetic Acid
Na	136-145	126	140	135	140	134	136	140	135
K	3.5-5.0	5.6	4	1.5	2	2.2	2.2	2	2
Ca	2.1-2.6	1.0	1.25	1.25	0.875	1.84	1.91	1.75	1.5
free [Ca2+]	[1.06]								
Mg	0.75-1.25		0.5	0.5	0.375	0	0	—	0.375
free [Mg2+]	[0.53]								
mEq Cations	142.7-153.2	133.6	147.5	140	144.5	139.88	142.02	145.5	140.75
Cl	100-106	109	120.7	105	106	107.28	103.82	107	106.5
HCO_3	26-28	23.9	26.8					33	33
Pi	1-1.45								
SO_4	0.32-0.94								
L-lactate	0.6-1.8								
pyruvate									
Lact/pyr									
D B OHbutyrate									
acetoacetate									
B HB/ acac									
acetate				35	38.5	32.6	38.2		
Other								2 HAcetate 23.5 gluconate	2 HAcetate
mEq anions	128.7-139.4	132.9	147.5	140	144.5	139.88	142.02	145.5	141.5
Na/Cl	1.28-1.45	1.16	1.16	1.29	1.32	1.25	1.31	1.31	1.27
Glucose or others	3.9-5.6	76-151	10	0	0	0	0	0	0
CO_2	0.99-1.39	0	1.24	0	0	0	0	~1.3	~1.3
pH	7.35-7.45	~8.6	7.4	~5.5-6.5	~5.5-6.5	~6.7	~6.7	~7.4	~7.4
mOsm	285-295	343-418	304.8	278.25	287.75	277.92	282.97	289.3	280.4

2 d 6. Kolff Wj. New Ways of Treating Uremia, J & A Chruchill, London, 1947
2 d 7. Murphy WP, Swan RC, Walter C, Weller JM, Merrill JP. J Lab Clin Med 40: 436, 1952. Essentially Krebs Henseleit, but with lower Mg and Ca.
2 a 16. Mion CM, Hegstrom RM, Boen ST. Scribner BH. Trans Am Soc Artif intern Organs 10: 110-113, 1964
2 a 17. Made in concentrates by numerous manufactures. The mean concentrations used are given in 2 d 17 according to Parsons FM and Stewart WK, listed above in title.
2 a 18. Bjaelder et al Nephron 27: 142-145, 1981. "Low" acetate leaves the patients acidotic, "high" acetate leaves them in normal. Bjaelder's interpretation for the reasons for the acidosis are incorrect.
2 b 6. Kraut J et al. Clin Neph 15: 181, 1981. Used HCO_3 and acetic acid.
2 b 3. Commercial source. CDBE Laboratories, 1201 Oak Street, Lakewood Colorado.

TABLE III

Prior Art Peritoneal Dialysis Solutions
The compilation of solutions are taken from: Facts and Comparison J.B. Lippincott, 111 West Port Plaza, Suite 423, St Louis, Mo. 63146, October, 1982, p. 705-706.
Indication: Acute renal failure or exacerbation of chronic renal failure; acute poisoning by dialyzable toxins; acute pulmonary edema; intractable peripheral edema; anasarca; endogenous intoxication such as hyperkalemia, hyperuricemia, hypercalcemia, and uremia; hepatic coma, especially with hepatorenal syndrome.

Product and Distributor	Dextrose g/Liter	Electrolyte content given in mEq/liter Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	Lactate	Acetate	mOsm/ Liter	Osmolarity How Supplied
Dianeal w/1.5% Dextrose(Travenol)	15	141		3.5	1.5	101	45		366	In 1000 and 2000 ml.
Dianeal PD-2 w/1.5% Dextrose (Travenol)	15	132		3.5	0.5	96	40		346	In 2000 ml.
Dianeal 137 w/1.5% Dextrose (Travenol)	15	132		3.5	1.5	102	35		347	In 2000 ml.
Inpersol w/1.5% Dextrose (Abbott)	15	132		3.5	1.5	99	35		344	In 1000 and 2000 ml.
Peridial 1 1/2-D (Cutter)	15	133		3.5	1.5	102	35		348	In 1000 and 2000 ml.
Peritoneal Dialysis w/1.5% Dextrose-Low Sodium (American-McGaw)	15	131		3.4	1.5	100	35		345	In 1000 and 2000 ml.
Dianeal K w/1.5% Dextrose	15	141	4	3.5	1.5	105	45		374	In 1000 ml.

TABLE III-continued

Prior Art Peritoneal Dialysis Solutions

The compilation of solutions are taken from: Facts and Comparison J.B. Lippincott, 111 West Port Plaza, Suite 423, St Louis, Mo. 63146, October, 1982, p. 705-706.

Indication: Acute renal failure or exacerbation of chronic renal failure; acute poisoning by dialyzable toxins; acute pulmonary edema; intractable peripheral edema; anasarca; endogenous intoxication such as hyperkalemia, hyperuricemia, hypercalcemia, and uremia; hepatic coma, especially with hepatorenal syndrome.

Product and Distributor	Dextrose g/Liter	Electrolyte content given in mEq/liter Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	Lactate	Acetate	mOsm/ Liter	Osmolarity How Supplied
(Travenol)										
Dianeal K-141 w/1.5% Dextrose (Travenol)	15	132	4	3.5	1.5	106	35		355	In 2000 ml.
Peritoneal Dialysis w/1.5% Dextrose-Potassium (American McGaw)	15	140	4	4.0	1.5	105		45	375	In 2000 ml.
Peritoneal Dialysis w/1.5% Dextrose (American McGaw)	15	141		4.0	1.5	103		45	370	In 1000 and 2000 ml.
Dianeal PD-2 w/2.5% Dextrose (Travenol)	25	132		3.5	0.5	96	40		396	In 2000 ml.
Dianeal PD-2 w/4.25% Dextrose (Travenol)	42.5	132		3.5	0.5	96	40		485	In 2000 ml.
Dianeal w/4.25% Dextrose (Travenol)	42.5	141		3.5	1.5	101	45		505	In 2000 ml.
Dianeal 137 w/4.25% Dextrose (Travenol)	42.5	132		3.5	1.5	102	35		486	In 2000 ml.
Inpersol w/4.25% Dextrose (Abbott)	42.5	132		3.5	1.5	99	35		484	In 2000 ml.
Peridial 4 1/2-D (Cutter)	42.5	133		3.5	1.5	102	35		487	In 2000 ml.
Peritoneal Dialysis w/4.25% Dextrose-Low Sodium (American McGaw)	42.5	131.5		3.4	1.5	100	35		485	In 2000 ml.
Dianeal K-141 w/4.25% Dextrose (Travenol)	42.5	132	4	3.4	1.5	106	35		494	In 2000 ml.
Peritoneal Dialysis w/4.25% Dextrose	42.5	141.5		4.0	1.5	103		45	510	In 2000 ml.
Peritoneal Dialysis Concentrate w/30% D* (American McGaw)	15	130		3.5	1.0	102		34.5	345	In 2000 ml.
Peritoneal Dialysis Concentrate w/50% D* (American McGaw)	25	130		3.5	1.0	102		34.5	395	In 2000 ml.
Peritoneal Dialysis Concentrate w/30% D* Low Sodium (American McGaw)	15	118.5		3.5	1.0	90.5		34	320	In 2000 ml.
Peritoneal Dialysis Concentrate w/50% D*	25	118.5		3.5	1.0	90.5		34	370	In 2000 ml.

*Concentration of formulation after dilution with 10 parts water.

EXAMPLE 42

The following example illustrates usage of Class I solutions for electrolyte and fluid therapy.

The most commonly used electrolyte solution used today, by those skilled in the art, is so called "physiological" salt, or "normal saline" by which is means 0.9% NaCl in H_2O in the U.S. or 0.95% NaCl in H_2O in the United Kingdom. (See Table IX solutions 1a1 and 1a2 respectively). These solutions, wherein the milliequivalent ratio of Na/Cl is 1, are distinctly different from normal human plasma wherein the ratio of Na/Cl ranges from 1.28 to 1.45 (*N.E.J.M.* 283, 1285, 1970). Infusion of such solutions has long been recognized to be undesirable leading to a pathological condition known as "hyperchloremic acidosis". (See Black D. A. K., *Lancet* 1, 353, 1953, and *Harrison's Textbook of Medicine*, pp 230 to 236, 1983). The degree of the pathology induced by solutions where the ratio of Na/Cl is below the ratio 1.28-1.45 depends upon:

(1) the quantity f solution infused relative to the volume and electrolyte content of the extra- and intracellular H_2O volume of the cells being contacted;

(2) the rate of infusion of solutions;

(3) the degree of existing pathology in the organism being contacted with such fluid;

(4) the efficiency of the kidney in excreting the excess of Cl^- over Na^+ being administered.

In this example, the replacement of plasma H_2O and salt content in the rat serves as a model stimulating the situation which might occur in a human patient when a severe burn over 50% of the body exists resulting in the loss of plasma H_2O and electrolytes into transudates and blisters over the surface of damaged skin. Three solutions for therapy will be used: standard 0.9% aqueous NaCl (composition 1a1 of Table IX), standard lactated Ringer's U.S. (composition 2a3 of Table X) and a modified redox-balanced Ringer's Lactate solution containing, with near-equilibrium couples, (l-lactate$^-$/-pyruvate$^-$ and D-betahydroxybutyrate$^-$/acetoacetate$^-$), HCO_3^-/CO_2 (composition 2b2 of Table X) in accord with the present invention. The composition of the 3 fluids are given in Table XIII below.

TABLE XIII

Composition of Fluids				(Electro2)
Units mmoles — L fluid	Normal Plasma N.E.J.M. 283, 1285 1970	1 a 1 Isotonic NaCl	2 a 3 Lactated Ringer's	2 b 2 R—B Lactated Ringer's HCO_3^-/CO_2
Na	136–145	155	130	130
K	3.5–5.0		4	4
Ca	2.1–2.6		1.5	1.5
free [Ca2+]	[1.06]			
Mg	0.75–1.25			
free [Mg2+]	[0.53]			
Σ mEq Cations	142.7–153.2	155	137	137
Cl	100–106	155	109	96
HCO_3	26–28			29
Σ Pi	1–1.45			
SO_4	0.32–0.94			
L-lactate	0.6–1.8		28 (d,l)	7
pyruvate				1
Lact/pyr			oo	7
D B OHbutyrate				3
acetoacetate				1
B HB/acac				3
acetate				
Other				
Σ mEq anions	128.7–139.4	155	137	137
Na/Cl	1.28–1.45	1.00	1.19	1.35
Glucose or others	3.9–5.6			
CO_2	0.99–1.39			1.5
pH	7.35–7.45	6.0	6.5	7.4
Σ mOsm	285–295	310	272	274

METHODS

250 fed male Wistar rats are each anesthetized and systematically burned with gasoline over approximately the lower 50% of the body surface. A blood sample is taken from each rat prior to administration of the burn, and then again two hours after the burn from a venous canula inserted into the saphenous vein. Each animal is placed in a restraining cage.

In the opposite saphenous vein, a canula is inserted to measure plasma electrolyte content. Five minutes after administration of each electrolyte solution, blood is drawn for electrolyte analysis. Each rat's liver is removed, freeze clamped and the redox and phosphorylation states of liver measured by the methods previously described by Veech et al. (*J. Biol. Chem.* 254, 6538–6547, 1979).

RESULTS AND DISCUSSION

It is observed that ½ hour after the gasoline burn, a series of weeping blisters develop over the lower ½ of each rat's body. The volume of the transudate within these blisters is estimated by measurement of area and thickness to contain 4 ml of transudate or ($250 \times 0.07 = 17.5$ ml blood volume) or about 40% of the rat's average total plasma volume. This deduction is confirmed by measurement of the rat hematocrit which is 55% while the Na^+ is 155 millimoles per liter plasma and Cl^- is 110 millimoles per liter plasma due to fluid loss. In the untreated controls rats, the hematocrit is 44%. Each treated animal's blood pressure is falling, heart rate is increasing, and urine output ceases.

Each treated animal is judged to be in hypo-volemic shock and 6 mls of the three different solutions are infused, by venous canula, over the next 10 minutes, into three different animals. Five minutes after completion of the infusion, electrolytes are drawn from the canula, the animals sacrificed, and the liver freeze clamped. The average blood electrolyte level, in each of the three groups of animals so infused, is shown in Table XIV below.

TABLE XIV

Composition of Plasma After Infusion				(Electro2)
Units mmoles/ L fluid	Normal Pasma N.E.J.M. 283, 1285, 1970	1 a 1 Isotonic NaCl	2 a 3 Lactated Ringers	2 b 2 R—B Lactated Ringers HCO_3^-/CO_2
Na	135–145	150	143	138
K	3.5–5.0	5	5	5
Ca	2.1–2.6	2.0	2.2	2.5
free [Ca^{2+}]	[1.06]			
Mg	0.75–1.25	1.0	1.0	1.0
free [Mg^{2+}]	[0.53]			

TABLE XIV-continued

Composition of Plasma After Infusion				(Electro2)
Σ meq Cations	142.7-153.2	158	153.2	147.5
Cl	100-106	123	105	102
HCO_3	26-28	18	13	27
Σ Pi	1-1.45	1.5	1.2	1
L-lactate	0.6-1.8	5.0	21	5
pyruvate		0.3	1.0	0.7
Lact/pyr			21	7
D-B—OH butyrate				2
acetoacetate				0.7
BHB/acac				3
acetate				
others				
Σ meq anions	128.7-139.4	146.3	141.2	138.65
Na/Cl	1.28-1.45	1.22	1.34	1.36
Glucose	3.9-5.6	8.2	10	7
or others				
CO_2	0.99-1.39	1.14	0.82	1.35
pH	7.35-7.445	7.30	7.30	7.4
Σ m OsM	285-295			

Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

It is observed that the animals given 1a1 (0.9% saline) solution each have hyperchloremic acidosis with a Na/Cl ratio of 1.22 and plasma pH of 7.30. The animals given solution 2a3 Ringer's Lactate solution each have lactic acidosis with a plasma pH of 7.3 and an elevated [lactate]/[pyruvate] ratio. Both groups of these animals have low serum [HCO_3] and have a compensated metabolic acidosis which requires that they hyperventilate off their CO_2. In contrast, the animals given solution 2b2 (Redox-balanced Ringers Lactate with HCO_3/-CO_2) each have a normal [lactate]/[pyruvate] ratio, a normal [HCO_3^-]/[CO_2] ratio and a normal plasma pH. More importantly, each of these animals achieves a replacement of H_2O and electrolytes as required for continued life, but without inducing an abnormal Na/Cl ratio, an abnormal redox state, or an abnormal phosphorylation potential. No change in respiratory pattern is observed in the grave life-threatening situation. Solution 2b2 is then an improvement over the state of the art.

In Table 3 is given the results of the freeze clamping of the liver to illustrate the effects of these solutions on the nucleotide ratios in liver cells. These results indicate that only in the liver cells of the rats treated with the redox-balanced Ringer's lactate solution (Table X, solution 2b2) of this invention do these ratios approach normal values. Here, it is seen that administration of Na/Cl in 1:1 ratio leads to no change in the cytoplasmic [NAD]/[NADH] but does cause an increase in the cytoplasmic [ATP]/[ADP][Pi]. With no intention to be bound by theory, the elevation of [ATP]/[ADP][Pi] would be expected from equation 7 given in another section. The conventional Ringer's lactate (2a3) gives a profound and pathological decrease in the cytoplasmic [NAD+]/[NAD] to levels associated with alcoholic fatty liver. There is, of course, a predictable falls in the [ATP]/[ADP][Pi], since the redox state of the cytoplasmic NAD-couple is directly and inversely linked to the cytoplasmic [ATP]/[ADP][Pi] ratio as equation 5 shows.

In contrast, the new Redox Balanced Ringer's Lactate solution of the present invention does not change the cytoplasmic [NAD+]/[NADH] from out of the normal range and causes no change in the [ATP]-/[ADP][Pi]. Replacement of needed H_2O and electrolytes has been accomplished without inducing acidosis or any other recognized pathologic effects which can be demonstrated by using NaCl in 1:1 ratio or standard Ringer's Lactate in this simulation of a very common clinical situation.

TABLE XV

Example 42
Case 1
Metabolite Contents of Freeze-Clamped Rat Liver in Rats After Infusion with Normal Saline, Ringer's Lactate, and Redox Balanced Ringer's Lactate with HCO_3^-/CO_2
Values are in μmoles/g wet weight.

	Normal Rat Solution	0.9% NaCl Infusion 1.a.1.	Ringer's Lactate 2.a.3.	New R-B Ringer's Lactate with HCO_3^-/CO_2 2.b.2
Glucose	7.3	8.0	13	8
Glucose 6-P	0.12	0.18	0.26	0.16
Dihydroxy-acetone-P	0.029	0.051	0.078	0.039
3-Phospho-glycerate	0.309	0.369	0.56	0.35
L-Lactate	0.444	0.812	14.8	5.2
Pyruvate	0.086	0.165	0.70	0.74
L-Lactate/pyr	5.16	4.92	21	7.00
3-PG/DHAP	10.65	7.24	7.14	8.93

TABLE XVI

Example
Case 1
Co-Factor Ratios of Freeze-Clamped Liver of Rat After Infusions with 0.9% Normal Saline, Ringer's Lactate, and Redox-Balanced Ringer's Lactate with HCO_3^-/CO_2

	Normal Rat	0.9% NaCl Infused Rat 1.a.1	Ringer's Lactate Infused Rat 2.a.3	R-B Ringer's Lactate with HCO_3^-/CO_2 2.b.2
Free Cytoplasmic [NAD+]/[NADH]	1750	1790	429	1290
Free Cytoplasmic	14,000	20,900*	5,000*	12,000

TABLE XVI-continued

Example Case 1 Co-Factor Ratios of Freeze-Clamped Liver of Rat After Infusions with 0.9% Normal Saline, Ringer's Lactate, and Redox-Balanced Ringer's Lactate with HCO_3^-/CO_2				
	Normal Rat	0.9% NaCl Infused Rat 1.a.1	Ringer's Lactate Infused Rat 2.a.3	R-B Ringer's Lactate with HCO_3^-/CO_2 2.b.2
$\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]}\ M^{-1}$				

*indicates change is significant at $p > 0.05$.

EXAMPLE 43

Use of Solutions for Parenteral Nutrition

The procedure used is identical to that utilized by Woods, Eggleston and Krebs in *Biochem. J.* (1970) 119, 501–510.

Animals and Diets

Female Wistar rats, each weighing 170–215 g, are obtained and are fed on a standard small-animal diet.

Reagents

D-Glyceraldehyde, 1-α-Glycerophosphate (dicylohexylammonium salt) having a purity of 96% of the calculate L-form and other substances, nucleotides, coenzymes, and crystalline enzymes.

Liver Perfusion

The method of liver perfusion used is that described by Hems, Ross, Berry & Krebs (1966). The perfusion medium is the physiological saline (Krebs & Henseleit, 1932), containing washed aged human erythrocytes. The bovine serum albumin is dialyzed as a 10% solution (at 4° C.) against three changes of physiological saline (Krebs-Henseleit) and gassed with CO_2+O_2 (5:95).

The perfusion medium described by Hems et al. (1966) is used, which contains initially about 1 mM l-lactate [0.87±0.05 S.E.M. (14) umol/ml] derived from the erythrocytes. To decrease the initial lactate concentration, the erythrocytes are washed five times with ten times their volume of physiological saline. This lowers the initial lactate concentration in the perfusion medium to 0.23±0.02 S.E.M. (16) umol/ml. The medium is gassed with CO_2+O_2 (5:95) during perfusion.

Into the perfusion of 150 ml is added a sufficient quantity of two parenteral nutrient solutions, one containing 10 mM D-Fructose from a commercial source (5% Fructose in Electrolyte #75, Travenol, *Facts and Comparison*, August '83, p52b) and a new parenteral solution composition using glucose in place of fructose, a normal Na:Cl ratio, redox-balanced lactate/pyruvate and excess K as does Electrolyte #75. Glucose enters the metabolic sequence at a "safe entry" point as herein defined. The composition of each solution is given in Table XVII below.

Sampling of Liver

For the analysis of liver, samples are rapidly frozen in vivo or during perfusion, by using the deep cooled clamps of Wollenberger, Ristau & Schoffa (1960). The resulting disc of liver tissue is ground to a fine powder in a cooled mortar with frequent additions of liquid N_2. The liver powder is transferred to a tared centrifuge tube cooled in liquid N_2 and 4 ml of icecold 6% (w/v) $HClO_4$ is then added to each gram of liver powder with constant stirring. The resulting slurry is allowed to thaw and then is homogenized in the centrifuge tube at a low speed with a glass pestle. The homogenate is kept ice-cold for 30 minutes, centrifuged, and the resulting supernatant is brought to pH 6–7 with 20% (w/v) KOH to precipitate the excess of $HClO_4$ as $KClO_4$. The assays are carried out on the clear supernatant.

Preparation of Liver Aldolase

Livers of large (300–450 g) rats are bled by perfusion in situ with cold isoosmotic KCl and then homogenized with 4 vol. of KCl. After centrifugation at 30000×g for 20 minutes, the supernatant is fractionated with $(NH_4)_2SO_4$ as described by Leuthardt & Wolfe (1955). The final precipitate is taken up in a small volume of water (0.3 ml/g of original liver) and dialyzed against 200 vol. of water at 0 C., changed every hour for 4 h. The cloudy preparation is centrifuged and 0.1 ml of 0.1M EDTA is added to every 4 ml of clear supernatant.

TABLE XVII

COMPOSITION OF FLUIDS			
UNITS	(1)	(2)	(3)
m moles/L			
Na	136–145	40	40
K	3.5–5.0	35	35
Ca	2.1–2.6		
free $[Ca^{2+}]$	[1.06]		
Mg	0.75–1.25		
free $[Mg^{2+}]$	[0.53]		
meq Cations	142.7–153.2	75	75
Cl	100–106	47.5	29
HCO_3	26–28		26
Pi	1–1.45	7.5	1.4
SO_4	0.32–0.94		
l-lactate	0.6–1.8	20(d,l)	15.64
pyruvate			1.56
Lact/pyr		(inf.)	10
d-Beta OH butyrate			
Acetoacetate			
Beta HB/acac			
Acetate			
Others			
meq anions	128.7–139.4	75	75
Na/Cl	1.28–1.45	0.84	1.36
Glucose	3.9–5.6		278
Fructose		278	
CO_2	0.99–1.39		1.5
pH	7.35–7.45	—	7.4
m OsM	285–295	428	429.5

Footnotes for Table 1
(1) Indicates: Normal Human Plasma as reported in N.E.J.M. 283, 1285, (1970).
(2) Indicates: 5 wt % Fructose in Electrolyte #75 (commercially available from Travenol as shown in "Facts & Comparisons" Aug. '83, p. 52b).
(3) Indicates 5% Glucose in Electrolyte Solution for parenteral nutrition from this patent following our outlines of safe entry points and a normalized Na/Cl ratio and redox state. Such a solution improves Solution 2 in this table.

Incubation for 1 h at 25° C. completely inactivated sorbitol dehydrogenase (EC 1.1.1.14) (Hers, 1956), which would otherwise react with fructose. The final preparation, containing 35–45 mg of protein/ml, is stored at −18° C. and is found to lose only about 30% activity in one year. In addition to aldolase activity, it also contains glycerol 1-phosphate dehydrogenase (EC 1.1.1.8) activity and triose phosphate isomerase (EC 5.3.1.1) activity.

Other Aldose Preparations

Chilled fresh rat and rabbit tissues are homogenized with 14 vol. of 1 mM-EDTA and centrifuged for 20

minutes at 30,000×g. The supernatant obtained is used in assays without further purification. A crystalline preparation of rabbit muscle aldolase is supplied by the Boehringer Corp. (London) Ltd.

Analytical Methods

ATP is determined by the method described by Lamprecht & Trautschold (1963), ADP and AMP are determined in the combined assay of Adam (1963). Pi was determined by the method described by Berenblum & Chain (1938) as modified by Martin & Doty (1949). Fructose 1-phosphate, is determined by the method of Eggleston (1970). Fructose 1,6 -diphosphate, is measured together with total triose phosphates in the combined assay of Bucher & Hohorst (1963); pyruvate, phosphoenolpyruvate, 2- and 3-phosphoglycerate are determined in sequence (Czok & Eckert, 1963). The references to other analytical methods are as follows: α-glycerophosphate (Hohorst, 1963b); L-(+)-lactate (Hohorst, 1963c); glucose 6-phosphate and fructose 6-phosphate (Hohorst, 1963c); glucose 1-phosphate (Bergmeyer & Klotzsch, 1963); glucose and fructose (Klotzsch & Bergmeyer, 1963); the sum of D-glyceraldehyde and glycerol (Pinter, Hayashi & Watson, 1967). For the fluorimetric determination of very low concentrations of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate by the method of Veech, Raijman, Dalziel & Krebs (1969), a portion of the neutralized supernatant is shaken for 1 minute with Florisil (100–200 U.S. mesh) to remove flavins and then recentrifuged before use. In livers perfused with fructose where the concentration of dihydroxyacetone phosphate is increased, it is determined by the spectrophotometric method of Bucher & Hohorst (1963). IMP is determined by a combination of paper chromatographic separation (Krebs & Hems, 1953) and a spectrophotometric assay. A portion of deproteinized liver extract (0.1 or 0.2 ml) is dried onto a 1 cm area on Whatman no. 1 chromatograph paper under a current of hot air. Duplicates, with and without added IMP standards (10 ul, 2 mM solutions) on the same spot, are developed by descending chromatography with the isobutyric acid-ammonia solvent mixture described by Krebs & Hems (1953) for 45–48 h at room temperature. After drying in a current of air, the papers are examined under u.v. light from a Chromatolite lamp (Hanovia Ltd., Slough, Bucks, U.K.) and absorbent areas are ringed by pencil. Average distances run from the starting line are: IMP 23 cm, ATP 27 cm, ADP 32 cm, AMP and inosine 37 cm. IMP areas, and a blank area of similar size before the starting line, are cut out and dropped into 4 ml of 10 mM potassium phosphate buffer, pH 7.0. After gentle mixing at intervals for 1 h, 3 ml is removed and the extinction at 248 nm in 1 cm wide silica cells in a Zeiss spectrophotometer is determined. At this wavelength, the Emax. $\times 10^3$ for IMP is 12.3 (Deutsch, 1952). Recovery of standards by the whose procedure is 93–104%.

RESULTS

The values of metabolites found in freeze clamped liver are given in Table XVIII.

TABLE XVIII

Liver Contents of Metabolites (After 10 Minutes of Perfusion)
Values Are In uMoles/g Wet Weight

	(1)	(2)	(3)
D-Glucose	6.99	2.29	10
D-Fructose	about 0	10	about 0

TABLE XVIII-continued

Liver Contents of Metabolites (After 10 Minutes of Perfusion)
Values Are In uMoles/g Wet Weight

	(1)	(2)	(3)
Glucose 6-P	0.25	0.14	0.30
Fructose 1-P	0.23	8.72	0.25
Dihydroxyacetone -P	0.04	0.16	0.04
3 Phosphoglycerate	0.26	0.16	0.26
Lactate	0.79	1.34	0.79
Pyruvate	0.08	0.15	0.08

Footnotes for Table XVIII
(1) Indicates liver before perfusion.
(2) Indicates perfusion with solution 1 from commercial sources.
(3) Indicates perfusion with solution 2 from this patient.

Infusion of a fructose solution at a rate sufficient to raise the blood fructose level to 1 mM drops liver and hence blood glucose level to 2.29 mM and raises fructose 1, P, over 35 fold to 8.7 umoles/g. In contrast, using a glucose solution so as to raise the blood level to 10 mM glucose has no appreciable effects except for a small elevation of glucose 6-P.

In Table XIX, we see that raising blood fructose causes a three fold drop in ATP and a seven fold increase in IMP. The phosphate is simply stripped off the nucleotides to put on fructose 1-P. In addition, the inorganic Pi in liver drops from 4.2. to 1.7 umoles/g weight. Taken together, this is a picture of profound metabolic disorder in intracellular energy metabolism which may be avoided by using the alternative NaCl balanced, redox-balanced solution which uses nutrients of the "safe entry point class".

TABLE XIX

Liver Content of Nucleotides and Pi
Values are in umoles/g wet weight

	Control	Fructose Solution (1)	Glucose Solution (2)
ATP	2.22	0.51	2.22
ADP	0.78	0.66	0.78
AMP	0.26	0.20	0.26
IMP	0.165	1.14	0.165
Pi	4.25	1.67	4.25
metabolically active Pi	13.75	13.88	13.80

In Table XX, we see the [NAD+]/[NADH] ratio calculated from the [l-lactate]/[pyruvate] ratio or the [malate]/[oxaloacetate] ratio increases with fructose by two fold. As predicted by the equation of the K_{G+G} reaction, this is accompanied by an incredible elevation of the free [ΣATP]/[ADP] [ΣPi] ratio to 150,000M^{-1}, the highest values ever recorded. Whether near-equilibrium is reached in such an abnormal situation is not the point here. Rather, it is clear fructose abnormally decreases not only the total amounts of the adenine nucleotides (Table XIX) but also severely distorts their thermodynamic relationship thereby profoundly disordering the normal metabolic state of liver. In contrast, solution 2 has no effect, firstly because it does not violate the "safe entry point" concept, and also, because it has pH, redox and NaCl balance.

TABLE XX

Example 2:
Using Class I Solutions for Parenteral Nutrition

	Liver Nucleotide Ratios		
	Control Liver	Liver Perfused with Parenteral Nutrient (1)	Liver Perfused with Parenteral Nutrient (2)
Free Cytoplasmic $\frac{[NAD^+]}{[NADH]}$	912	1812	912
Free Cytoplasmic* $\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]}$ M^{-1}	11,517	151,000	11,517

*The free cytoplasmic $\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]}$ is calculated from equation 5 in this disclosure as described by Veech R. L. et al, J. Biol. Chem. 254, 6538-6547, 1979.

The example also illustrates the concept of "safe entry points" discussed herein: Compounds which may be included in solutions which directly contact living cells, without, for instance, first passing through the gut wall to be metabolically changed, constitute the group herein herein identified by having "safe entry points". Members of the "safe entry point group" where levels over 3 mM may be used in fluids directly contacting cells are:

$\frac{\text{l-Lactate}}{\text{pyruvate}}$

$\frac{\text{d B-Hydroxybutyrate}}{\text{acetoacetate}}$

D-Glucose

The upper limits to which even these may be used depends upon the metabolite and medical situation and no upper limit can be set absolutely without such considerations. However, the sum of lactate and pyruvate is generally in the level of 10-12 mM in healthy, jogging adults. The sum of betahydroxybutyrate and acetoacetate is in the range 5-7 mM/L plasma in healthy individuals undergoing reducing three day fasts. (See Cahill G. F. and Aoki T. T. in *Cerebral Metabolism and Neural Function* (1980) Passonneau J. V., Hawkins R. A., Lust W. D. and Welsh F. A. eds; pp 234-242, Williams & Wilkins, Baltimore). Such levels may therefore be considered to be in a "normal" range and used safely in most normal conditions excepting perhaps ketones in pregnant women where the decision by the physician will depend upon the medical necessity. (See Rudolf M. C. J. and Sherwin R. S., *Clinics in Endocr. & Metab.* 12, pp 413-428, 1983).

The toxicity of elevating blood glucose above 13 mM/l is well documented in the studies of the University Diabetes Group and must be balanced in the physician's judgment by the need for calories in the patient. Glucose is herein demonstrated, however, to be much less toxic than fructose.

Compounds which may not be used parenterally as "safe entry points" into the metabolic sequence, as currently practiced in the art, are:

Acetate
Glycerol
Lactate (without pyruvate)
Pyruvate (without lactate)
Fructose

The methods used in this example are found in the following reference: Woods HF, Eggleston LV, Krebs HA. The cause of the accumulation of fructose 1-P on fructose loading. *Biochem J* 119: 501-510, 1970.

EXAMPLE 44

Use of Class II Solutions for Peritoneal Dialysis

The procedure used here in similar to that utilized by Klim and Williamson in *Biochem. J.* (1982) 214, 459-464.

Materials

Animals

Male Wistar rats weighing 213+35 g (66), at time of death, are used; there are no significant differences between the mean body weights of the experimental groups. They are maintained on a standard small animal diet, and water ad libitum in an animal house with lights on from 08:00 to 20:00 h. Chronic uremia is induced by the five-sixths bilateral nephrectomy technique (Morrison, 1966). Uremic rats are allowed approximately 14 days to recover from the last operation before use.

Peritoneal-Dialysis Solutions

A commercial peritoneal dialysis solution is used, containing 45 mM acetate and 1.5% glucose (83 mM) and compared to a new dialysis solution of the present invention (Example 3). The composition of the two solutions is comparatively shown in Table XXI. Control rats are simply given glucose to raise their blood levels to those occurring in dialyzed animals.

The methods of measurement of liver metabolites are those of Veech and are described amply in the literature such as Veech et al. *J. Biol. Chem.* 254, 6538-6547, 1979; Veech, Eggleston & Krebs *Biochem. J.* 115, 609-619, 1969 and Veech et al. *FEBS Letts.*, 117, K65-72, 1980.

TABLE XXI

	Composition of Dialysis Fluids		
Units m moles L Fluid	Normal Plasma (1)	Commercial Fluid (2)	New Fluid (3)
Na	136-145	140	140
K	3.5-5.0	4	4
Ca	2.1-2.6	2.0	2.0
free $[Ca^{2+}]$	[1.06]		
Mg	0.75-1.25	0.75	0.75
Sigma mEq. Cations	142.7-153.2	150	150
Cl	100-106	105	105
HCO_3	26-28		29
Sigma Pi	1-1.45		
SO_4	0.32-0.94		
L-lactate	0.6-1.8		8.21
pyruvate			1.79
Lact/pyr			4.6
D-Beta-OH butyrate			3.24
Acetoacetate			2.76
BetaHB/acac			1.17
Acetate		45	
Sigma mEq anions	128.7-139.4	150	150
Na/Cl	1.28-1.45	1.33	1.33
Glucose	3.9-5.6	83	83
CO_2	0.99-1.39		1.5
pH	7.35-7.45	5.5-6.5	7.4

TABLE XXI-continued

Units m moles L Fluid	Composition of Dialysis Fluids: Normal Plasma (1)	Commercial Fluid (2)	New Fluid (3)
Sigma m OsM	285–295	379.75	379.75

Footnotes for Table I

(1) indicates: Normal plasma N.E.J.M. 283, 1285, 1970.

(2) indicates: Commercial Fluid-Peritoneal dialysis with 1.5% Glucose. American McGaw, Facts and Comparisons, October 1982, page 704.

(3) indicates: New fluid-improved peritoneal dialysis fluid formulated in this disclosure is meant to mimic the ideal commercial fluid. This new fluid is not to be taken as "ideal" but is simply a way of illustrating why acetate should not beused. A better fluid would also contain HCO_3/CO_2. Lactate/pyr & Beta-HB-/AcAc but would have an increased Na:Cl ratio of between 1.38 to 1.41 to increase alkali reserve in the chronically acidotic uremics. Cl^- could be 100, HCO_3^- of 34 with $[CO_2]$ of 1.7 mM as an example of a fluid designed in conformity with the principles outlined herein. Such fluids have (1) redox balance and hence normal phosphorylation state achieved with (2) pair of ratioed couplesso as to achieve a normal M desired Na:Cl ratio (3) while causing less pathological consequences than present art allows.

The values of metabolites in rat liver are given after seventy minutes of peritoneal dialysis in Table XXII.

TABLE XXII

N	Control (13)	(1) Acetate Peritoneal Dialysis (10)	(2) Redox-Balanced Dialysis Fluid (10)
Values are given in n moles/g wet weight liver.			
Dihydroxy-acetone P	46 ±3	53 ±5	69
3-Phospho-glycerate	294 ±15	405 ±27	294
l-Lactate	727 ±36	743 ±70	6081
Pyruvate	158 ±13	98 ±9	1326
d-Beta Hydroxy-butyrate	117 ±20	151 ±12	2400
Acetoacetate	100 ±19	117 ±8	1380
Acetate	20	33000	20

In Table XXIII are given the changes in liver content of divalent cations, Pi, PPi and total metabolizable phosphate containing compounds after such treatment:

Na Acetate currently account for about of 80% of hemodialysis in the United States. The increased Pi demonstrated herein during acetate dialysis is "hidden" in liver and flows out (into blood) after dialysis accounting for why such patients remain persistently hyperphosphotemic leading to much current pathology found in chronic dialysis patients.

The data presented in Table XXIII clearly show that peritoneal dialysis, with acetate containing fluids, leads to gross elevations of liver inorganic pyrophosphate and liver calcium. While not widely appreciated, inorganic pyrophosphate (PPi) is an important controller of cellular metabolic pathways of many types. See *Lawson J. W. R.* et al. in *Gluconeogenesis*, 1976 (Hanson R. W. & Mehlman M. A. Eds) pp 481–511, John Wiley & Sons, New York). Changes in PPi are therefore likely to be of widespread signficance. The 70% increase in liver calcium is, of course, clearly large and of potential significance because of the importance calcium plays as an activator of many intracellular protein kinases.

Finally, Table XXIII shows that acetate induces a rapid increase of 4.2 umoles/g wet weight of the liver's rapidly metabolizing phosphate compounds. It derives this excess ΣPi from the blood and other phosphate stores. When the acetate is finally metabolized, this phosphate returns to the blood where Pi is 1–1.45 mM. Since liver and blood are roughly equal in weight in the normal adult, this movement of ΣPi out of liver must inevitably lead to the hyperphosphatemia which is a major and persistent pathological sequalae of uremia treated by current dialysis practice. This persistent elevation of blood Pi leads to chronic hyperparathyroidism, hypocalcemia, accelerated bone disease, ectopic calcification of tissue and many other causes of morbidity and even mortality in chronic renal disease. Because the phosphate accumulates in the liver during acetate dialysis, it is effectively "hidden" from the beneficial effects which dialysis is trying to obtain, namely the removal of excess dietary ΣPi which is taken in by the patient during the intradialysis periods.

TABLE XXIII

	Changes in Mg, Ca, Pi and PPi Content in Rat Liver During Dialysis. Values in umoles/g wet weight liver. Control (16)	(1) Acetate Dialysis (16)	Change Induced by Acetate Dialysis	(2) New Dialysis	Change Induced by new Dialysis
Ca	1.06	1.76	+.70	1.06	0
Mg	11.76	12.94	+1.18	11.8	0
Inorganic Pyrophosphate (PPi)	.018	0.198	+0.18	0.018	0
Inorganic Phosphate (Pi)	3.19	4.55	+1.36	3.19	0
Sigma Adenine Nucleotides	7.95	9.43	+1.48	7.95	0
Sigma Guanine Nucleodites	1.56	1.97	+0.41	1.56	0
Sigma Glycolytic Pi	0.65	1.65	+0.06	0.85	+.2
Sigma Metabolic Pi from all measured Metabolites	13.75	17.97	+4.22	13.95	+.2

It should be remembered that normal hemodialysis with 35 mM acetate makes the abnormal elevation in PPi reach 100 times normal with a quadrupling of liver Ca at the expense of bone stores of calcium. It is thus exaggerated in every way. Solutions containing 35 mM

TABLE XXIV

Table XXIV gives the results obtained for the redox and phosphorylation states calculated, as described in Equations 4 and 5. Values are given as means + S.E.M.

N	Control (5)	(1) Acetate Dialysis (6)	(2) New Dialysis (6)
Cytoplasmic free $\frac{[NAD^+]}{[NADH]}$	1944 + 94	1209* + 88	about 1944
Mitochondrial free $\frac{[NAD^+]}{[NADH]}$	18.2 + 2.3	17.4 + 2.6	about 18.2
cytoplasmic $\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]}\ M^{-1}$	25,800 + 3,200	13,700* + 2,600	about 25,800

*Indicates significant difference at $P > 0.05$.

The use of acetate in a peritoneal dialysis fluid obviously causes a significant decreased in the free cytoplasmic [NAD+]/[NADH] and an even more profound decrease in the cytoplasmic [ΣATP]/[ΣADP][ΣPi] ratio. This is so because the free [NAD+]/[NADH] ratio of cytoplasm is directly linked to the free cytoplasmic [ΣATP]/[ΣADP][ΣPi] by equation 5. (see Veech, et al., *J. Biol. Chem.* 254, 6538-6547, 1979). On page 704 of *Facts and Comparisons*, October, 1982, are listed 16 peritoneal dialysis solutions, using 35 to 45 mMolar (d,l)-lactate in commercial peritoneal dialysis solutions made by four different commercial manufacturers. These solutions, in addition to the 7 commercial acetates containing peritoneal dialysis solutions, make up the current state of the art. None achieve the normal Na/Cl ratio they desire in the manner described herein.

No example of the effects of using 35 to 45 mM L-lactate alone, in a peritoneal dialysis solution, need be given. It is by now obvious, from the teachings here presented, that such solutions are entirely without redox balance but indeed induce a profound lactic acidosis with a pathological decrease in the free cytoplasmic [NAD+]/[NADH] and the free cytoplasmic [ATP]/[ADP][Pi] to which it is linked by equation 5. It is also obvious that redox-balanced solutions, made by the principles outlined herein, would be an advance in the present art.

EXAMPLE 45

Hemodialysis

Using hemodialysis equipment, which is the current major type in use, (see Keshaviah et al., *CRC Critical Reviews in Biomedical Engineering* 9, 201-244, 1983) and using the most common type of dialysis fluid currently in use in the art, which uses between 35 to 45 mMoles/L of Na acetate to correct the anion gap, (see Parsons, F. M. & Stewart, W. K., *The Composition of Dialysis Fluid in Replacement of Renal Function by Dialysis*, 2nd edition (1983) (Drukker W., Parsons F. M. & Maher J. F., eds) pp 148-170, (Martinus, Nijhoff, Hingham) we may obviously predict the effects, upon body organs such as the liver, of such treatment.

Methods

Rats are made uremic as described in the previous example. After five days, they are fasted, attached to a miniature hemodialysis apparatus, heparinized and dialyzed with two different solutions, one representing the most common types of currently used hemodialysis solutions, and another where the anion gap is made up without the use of HCO_3^-/CO_2, but instead, with the use of L-lactate/pyruvate and D-B-Hydroxybutyrate/acetoacetate as are given in the class 2-a solutions in this disclosure, as for example 2-a-8, Redox-Balanced Ringers. It should be understood that I do not conclude such a solution as 2-a-8 is the best solution for such a purpose, but I shall show it is superior to the existing art and may be used in the bulk of existing apparatus which contain deaerators* and currently use acetate containing hemodialysis fluids. (Keshaviah et al. *CRC Critical Reviews in Biomedical Engineering* 9, 201-244, 1983.) A few current machine, typically 1 out of 10 in the dialysis centers I have surveyed have dialysis machines of the type described by Miller J. H. et al. *Trans Am Soc artif Internal Organs* 25, 404-408, 1979. Such machines can use HCO_3^- containing solutions. Such HCO_3^-/CO_2 solutions are preferred.

The compositions of the two example solutions are given in Table XXV.

TABLE XXV

Example 4
Solution for Hemodialysis of a Uremic Rat.

Units	Normal Plasma N.E.J.M. 283, 1285	(1) Usual Hemodialysis Solution	(2) Redox-Balanced Hemodialysis Solution
mmoles — L fluid	1970		
Na	136-145	130-135	130
K	3.5-5.0	0-1.5	4
Ca	2.1-2.6	1.25	1.5
free [Ca2+]	[1.06]		
Mg	0.75-1.25	0.5	—
free [Mg2+]	[0.53]		
Σ mEq Cations	142.7-153.2	133.5-140	137
Cl	100-106	100.5	96
HCO_3	26-28		
Σ Pi	1-1.45		
SO_4	0.32-0.94		
L-lactate	0.6-1.8		32.1
pyruvate			1.9
Lact/pyr			17
D B OHbutyrate			5
acetoacetate			2
B HB/acac			2.5
acetate		33.5-40	
Other			
Σ mEq anions	128.7-139.4	133.5-140	137
Na/Cl	1.28-145	1.29-1.34	1.35
Glucose or others	3.9-5.6	0-101	0
CO_2	0.99-1.39	0	0
pH	7.35-7.45	~6.5	~6.5
Σ sOsm	285-295	270.25 to 375	272.5

(1) The composition of the usual hemodialysis solution is taken from Parson's and Stewart, 1983, cited above.
(2) Composition of solution 2-a-8 is taken from this application except that the lactate/pyruvate ratio is decreased to 17 to accomodate the absence of glucose since most current hemodialysis fluids use acetate without glucose. This composition is chosen to compare with current acetate hemodialysis practice. This solution should not be taken as "ideal" or even as recommended, but rather illustrative.

The rats are dialyzed with solutions 1 and 2 for four hours; the animals are sacrificed and the livers freeze clamped. A group of normal rats, starved 48 hours, are also sacrificed and their livers freeze clamped to serve as controls. Metabolites are measured, as previously described.

In Table XXVI, we see that both acetate and new redox-balanced dialysis fluids elevate liver sugar and the first portion of the gluconeogenic pathway. During acetate dialysis, changes occur throughout the gluconeogenic sequence and the ratio of one metabolite to another changes.

TABLE XXVI

Liver Metabolites from Rats Dialysed with Acetate Dialysis Fluid versus New Redox-Balanced Dialysis Fluids without HCO_3^-/CO_2
Values are given as means + S.E.M. in nmoles/g wet weight. A * indicates a significant difference from normal rats at $P < 0.05$ as judged by Student's T Test.

	Untreated Starved Rats	Commercial Acetate Dialysis	New Redox-Balanced Dialysis
N	13	10	
10^{-3} × glucose	4.81 + 0.21	7.94 + 0.42	7.2*
glucose 6-P	59 + 2	99* + 10	88.5*
glucose 1-P	7 + 1	11* + 1	10.5*
fructose 6-P	17 + 1	32* + 3	25.2*
fructose 1,6 bis-P	4.6 + 0.4	23* + 6	6.9
DHAP	11 + 1	36* + 4	16.5
3-phosphoglycerate	156 + 14	581* + 62	234
PEP	73 + 5	330* + 40	110
pyruvate	10 + 1	27* + 6	1260*
L-lactate	171 + 17	721 + 208	21300*
L-malate	268 + 28	592* + 84	402
α-ketoglutarate	118 + 13	86 + 17	177
isocitrate	17 + 2	41* + 3	25.5
citrate	308 + 42	944* + 85	462
acetoacetate	638 + 33	643 + 66	1330*
D-B OHbutyrate	1643 + 75	983* + 83	3300*
UDP-glucose	350 + 15	367 + 25	350
UTP	205 + 9	186 + 8	205
acetate	20	25000	20

In Table XXVII are presented the changes in the controlling co-factor ratios after the two types of dialysis.

TABLE XXVII

Free Nucleotide Ratios in Freeze Clamped Rat Liver After Acetate and Redox-Balanced Hemodialysis
Values are given as mean + S.E.M. An * indicates a significant difference from control values of $P < 0.02$ as judged.

(n)	Starved Control (13)	Acetate Dialysis (10)	Redox-Balanced Dialysis
Cytoplasmic $\frac{[NAD^+]}{[NADH]}$	587 + 86	391 + 35	587
10^3 × $\frac{[NADP^+]}{[NADPH]}$	7.3 + .7	2.1* + .3	7.3
$\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]}$ M^{-1}	3710 + 580	2090 + 280	3710
mitochondrial $\frac{[NAD^+]}{[NADH]}$	8.1 + 0.7	13.8* + 1.4	8.1

In Table XXVII we see that acetate dialysis causes oxidation of the mitochondrial [NAD+]/[NADH] ratio and reduction of the free cytoplasmic [NADP+]/-[NADPH] ratio while redox-balanced dialysis causes no changed as judged by the isocitrate/α-ketoglutarate ratio.

In Table XXVIII are presented the results of the measurement of the Ca, Mg, phosphate and pyrophosphate content of rat liver after acetate versus redox-balanced hemodialysis.

TABLE XXVIII

Changes in Mg, Ca and Phosphate Compounds in Liver Following Acetate versus Redox-Balanced Hemodialysis.

	Control	Acetate Hemodialysis	Redox-Balanced Hemodialysis
n	13	10	
Ca	1.33	+2.89	0
Mg	10.1	+1.8	0
PPi	0.024	+2.00	0
Pi	4.22	+3.73	0
Σ Adenine Nucleotide Pi	9.32	+0.07	0
Σ Guanine Nucleotide Pi	1.76	+0.19	0
Σ Glycolytic Pi	0.36	+0.86	+.50
Σ Pi Increased from All measured metabolites	15.71	+8.85	+.50

We see in Table XXVIII that acetate dialysis raises inorganic pyrophosphate 200 times while redox-balanced dialysis makes no change. Acetate hemodialysis increases liver calcium three fold; redox-balanced dialysis makes no change. Acetate hemodialysis increases total liver metabolizable phosphate by 8.8 m moles/g, while redox-balanced dialysis increases liver metabolizable phosphate by only 0.5 m moles/g, or 16 times. The "hidden" phosphate, inaccessible to dialysis after acetate hemodialysis, is the largest ever seen. The metabolic pathology is therefore even greater than that seen in Example 44.

EXAMPLE 45

Solutions of this invention when administered not only regulate redox state and phosphorylation, but also further tend to normalize the following states:

(1) Distribution of water between intracellular and extracellular fluid.

(2) Distribution of the inorganic electrolytes Na^+, K^+, Cl^-, and Ca^{2+} between intracellular and extracellular fluid, and

(3) Transmembrane cellular potential. ΔE

The following equations state the governing scientific laws involved:

0. Eqn 0 - The Second Law
J. Willard Gibbs. On the equilibrium of heterogeneous substances. J Conn Acad Sci 1876: III: 343.

0-1 Definition of Gibbs Free Energy and Other Properties of State:
$G = H - TS$
where:
G ~ Gibbs free energy
H ~ Enthalpy or heat content
T ~ absolute temperature
S ~ Entropy, or state of randomness or disorder

0-1a Entropy may be more rigorously defined by statistical and quantum mechanics in the Boltzmann Equation:
$S = k_B \ln\Omega$
where:
S ~ Entropy

k_B ~ Boltzmann constant $= \frac{R \text{ (gas constant)}}{\text{Avagadro's number}} = 1.38 \times 10^{-23}\ J/^\circ K.$

Ω ~ Degeneracy

0-2 $\Delta G = \Delta H - T\Delta S$
where ~ change in

-continued

0-3 Standard Free Energy ~ $\Delta G'$

$$\Delta G = \Delta G' + RT \ln \frac{[\text{products}]}{[\text{reactants}]}$$

where:
R ~ gas constant
= 1.987 calories/°K./mole and °K. ~ 273 + °C.
T = °K.
ln ~ 2.303 $\log_{10}$

0-3a $\Delta G' = -RT \ln K_{eq}$
where:

$$K_{eq} \sim \frac{[\text{products}]}{[\text{reactants}]}$$

0-4 At equilibrium, $\Delta G = 0$, so in $A + B \longleftrightarrow C + D$

$$\Delta G = -RT \ln K_{eq} + RT \ln \frac{[C][D]}{[A][B]}$$

where:
[ ] ~ activity or ~ concentration

"A theory is the more impressive the greater the simplicity of its premises, the more different are the kinds of things it relates, and the more extended is its range of applicability . . . It is the only physical theory of universal content which I am convinced, that within the framework of applicability of its basic concepts, will never be overthrown.

A. Einstein

I Eqn 1 - The Henderson-Hasselbalch Equation
The major buffer and controller of extra- and intracellular pH.
Henderson LJ. Blood, A Study in General Physiology. Silliman Lectures, Yale University Press, 1928

1.a
$$pH = pK_{a'} + \log \frac{[HCO_3^-]}{[CO_2]}$$

where:
$pK_{a'}$ = 6.10 at 38° C. and serum concentrations of electrolytes

1.b The solubility of CO_2 in fluid, i.e. dissolved CO_2 gas plus H_2CO_3 from:

$$CO_2 + H_2O \longleftrightarrow H_2CO_3$$

$$[CO_2] \text{ in mmol/liter} = \frac{pCO_2 \text{ in mmHg}}{760 \text{ mmHg}} \cdot \frac{\alpha \text{ml } CO_2/\text{ml of } H_2O}{22.26 \text{ L/mole}} \cdot \frac{1000 \text{ mmol}}{\text{mole}}$$

α_{CO_2} = 0.553/ml serum H_2O at 38° C. from:
Van Slyke DD. J Biol Chem 73: 765-799, 1928.

1.c The pH of a bicarbonate containing solution to which has been added a carbocylic acid such as acetic, lactic, acetoacetic acid with a pK' in the 3 to 4 range and where the concentration of HCO_3 is much larger than the concentration of carboxcylic acid:

$$pH = pK_{a'} - \log\left(\frac{[HCO_3^-]}{2([HCO_3^-] - [HA])} - \frac{1}{2} \right)$$

Thus adding 1.8 mM Hlactate and 0.2 mM Hpyruvate to 25 mM $NaHCO_3$ yields what pH?

$$pH = pK_{a'} - \log\left(\frac{[25]}{2([HCO_3 - [HA])} - \frac{1}{2} \right)$$

= 6.1 − (1.36)
= 7.46

-continued

II Donnan Equilibrium Equation
Donnan FG. Z Electrochem 17: 572, 1911
Donnan FG. Chem Rev 1: 73-90, 1924.

1. From Gibbs (Eqn 0)

$$RT \ln \frac{[Cl^-]_1}{[Cl^-]_2} + RT \ln \frac{[Na^+]_1}{[Na^+]_2} = 0$$

$$\left.\begin{matrix} 1 \\ \\ 2 \end{matrix}\right\} \Delta p \quad \overset{\Delta E}{}$$

$$\begin{matrix} [Na^+]_1 \rightleftharpoons [Na^+]_2 \\ [Cl^-]_1 \rightleftharpoons [Cl^-]_2 \\ Z[A^{z-}]_1 \searrow \end{matrix}$$

[ ] ≅ activity ≅ concentration
A ≅ non-diffusable polyanion
Z ≅ valance of polyanion

Or:

1.a $$\frac{[Cl^-]_1}{[Cl^-]_2} = \frac{[Na^+]_2}{[Na^+]_1}$$

Therefore: $$\frac{[Cl^-]_1}{[Cl^-]_2} = \frac{[Cl^-]_2}{[Cl^-]_1 + Z[A^{z-}]_1} = \frac{[Na^+]_2}{[Na^+]_1}$$

and for polyvalents:

$$\left(\frac{[\text{Anions}]_1}{[\text{Anions}]_2} \right)^{1/z \text{ anions}} = \left(\frac{[\text{Cations}]_2}{[\text{Cations}]_1} \right)^{1/z \text{ cations}}$$

2. From the Law of Electrically Neutrality:
$[Na^+]_2 = [Cl^-]_2$
$[Na^+]_1 = [Cl^-]_1 + Z[A^{z-}]_1$

3. Quadratic equation:

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Example: Consider albumin dialysed against 100% CO_2/3.13 $NaHCO_3$ buffer with 1.17 mM albumin (i.e. 8% solution). Hypothetically keep charge on albumin at −20/mole.

$$\frac{[HCO_3^-]_i}{[HCO_3^-]_o} = \frac{[HCO_3^-]_o}{[HCO_3^-]_i + 20[Alb^{-20}]} = \frac{[Na^+]_o}{[Na^+]_i}$$

$$\frac{[HCO_3^-]_i}{[3.13 \times 10^{-3}]} = \frac{[3.13 \times 10^{-3}]}{[HCO_3^-]_i + 20[1.17 \times 10^{-3}]}$$

$[HCO_3^-]_i = 0.4 \times 10^{-3}$M

II Eqn 2 Multicomponent Donnan Equilibrium System for Solutions Such as the Hemodialysis of Blood Plasma Electrolytes:
where $\Delta p = 0$ and all components but albumin are permeant. Subscript $_o$ ~ in dialysis fluid, subscript $_i$ ~ in patient's plasma, Δp ~ difference in pressure.

2.a. $$\frac{[Na^+]_i}{[Na^+]_o} = \frac{[K^+]_i}{[K^+]_o} = \left| \frac{[Ca^{2+}]_i}{[Ca^{2+}]_o} \right|^{\frac{1}{2}} = \left| \frac{[Mg^{2+}]_i}{[Mg^{2+}]_o} \right|^{\frac{1}{2}} =$$

$$\frac{[Cl^-]_o}{[Cl^-]_i} = \frac{[HCO_3^-]_o}{[HCO_3^-]_i} = \left| \frac{[Pi]_o}{[Pi]_i} \right|^{1/1.8} = \frac{[lac^-]_o}{[lac^-]_i} =$$

-continued

$$\frac{[pyr^-]_o}{[pyr^-]_i} = \frac{[acac^-]_o}{[acac^-]_i} = \frac{[BHB^-]_o}{[BHB^-]_i} = \frac{[acet^-]_o}{[acet^-]_i}.$$

Statement of electrical neutrality on two sides of an uncharged membrane

2.b.1. $[Na^+]_o + [K^+]_o + 2[Ca^{2+}]_o + 2[Mg^{2+}]_o = [Cl^-]_o + [HCO_3^-]_o + 1.8[Pi^{-1.8}]_o + [lac^-]_o + [pyr^-]_o + [acac^-]_o + [BHB^-]_o + [acet^-]_o$

2.b.2. $[Na^+]_i + [K^+]_i + 2[Ca^{2+}]_i + 2[Mg^{2+}]_i = [Cl^-]_i + [HCO_3^-]_i + 1.8[Pi^{-1.8}]_i + [lac^-]_i + [pyr^-]_i + [acac^-]_i + [BHB^-]_i + [acet^-]_i + Z[prot^{z-}]_i$

Distribution of cations on two sides of the membrane:

2.c

$$[K^+]_i = [K^+]_o \frac{[Na^+]_i}{[Na^+]_o}; [Ca^{2+}]_i = [Ca^{2+}]_o \left| \frac{[Na^+]_i}{[Na^+]_o} \right|^2;$$

$$[Mg^{2+}]_i = [Mg^{2+}]_o \left| \frac{[Na^+]_i}{[Na^+]_o} \right|^2$$

Distribution of Anions:

2.d

$$[Cl^-]_i = \frac{[Na^+]_o}{[Na^+]_i} [Cl^-]_o; [HCO_3^-]_i = \frac{[Na^+]_o}{[Na^+]_i} [HCO_3^-]_o;$$

$$[acet^-]_i = \frac{[Na^+]_o}{[Na^+]_i} [acet^-]_o; [Pi]_i = \left| \frac{[Na^+]_o}{[Na^+]_i} \right|^{1.8} [Pi]_o;$$

$$[lac^-]_i = \frac{[Na^+]_o}{[Na^+]_i} [lac^-]_o; [pyr^-]_i = \frac{[Na^+]_o}{[Na^+]_i} [pyr^-]_o;$$

$$[acac^-]_i = \frac{[Na^+]_o}{[Na^+]_i} [acac^-]_o; [BHB^-]_i = \frac{[Na^+]_o}{[Na^+]_i} [BHB^-]_o$$

Now solving for $[Na^+]_i/[Na^+]_o$ for a dialysis fluid$_o$ of known composition:

2.e

$$\frac{[Na^+]_i}{[Na^+]_o} [Na^+]_o + [K^+]_o + \frac{2[Na^+]_i}{[Na^+]_o} [[Ca^{2+}]_o +$$

$$[Mg^{2+}]_o] = \frac{[Na^+]_o}{[Na^+]_i} [Cl^-]_o + [HCO_3^-]_o + [acet^-]_o +$$

$$[lact^-]_o + [pyr^-]_o + [acac^-]_o + [BHB^-]_o +$$

$$1.8 \left| \frac{[Na^+]_o}{[Na^+]_i} \right|^{0.8} [Pi]_o + \frac{[Na^+]_i}{[Na^+]_o} |Z|[prot^{z-}]$$

and:

2.f

$$\frac{[Na^+]_o + [K^+]_o}{[Na^+]_o^2} [Na^+]_i^2 +$$

$$\frac{2([Ca^{+2}]_o + [Mg^{2+}]_o)}{[Na^+]_o^3} [Na^+]_i^3 - |Z| \frac{[prot^{z-}]}{[Na^+]_o} [Na^+]_i -$$

$$(1.8[Pi]_o[Na^+]_o^{0.8})[Na^+]_i^{(-0.8)} = [Cl^-]_o + [HCO_3^-]_o + [acet^-]_o + [lact^-]_o + [pyr^-]_o + [acac^-]_o + [BHB^-]_o$$

Plasma [concentration] ~ 0.935 × plasma H_2O [concentration]

III Eqn 3. Nernst Equation - ΔE

Nernst W. Theoretical Chemistry 4th Edition, 1904, McMillan, London. See also Silliman Lecture, 1906, Yale U. Press, New Haven.

3.

$$\Delta E = -\frac{RT}{nF} \ln \frac{[anion^-]outside}{[anion^-]inside}$$

or:

$$\Delta E = -\frac{RT}{nF} \ln \frac{[cation^+]inside}{[cation^+]outside}$$

where:
at 38° C. $T \sim 311°$ K.
R, the gas constant ~ 8.314 joules/degree/mole
n ~ number of equivilents
F, the Faraday, ~ 96,494 coulombs
ΔE ~ potential in volts
To convert ln to $\log_{10}$ multiply by 2.303
From Cornell N, Anal Biochem 1980; 102: 326-331, for isolated hepatocytes from starved rats incubated in Krebs-Henseleit.

$$\Delta E = -0.0617 \log \frac{[0.128 \text{ M } Cl^-]outside}{[0.041 \text{ M } Cl^-]inside}$$

$\Delta E = -0.0305$ V or -30.5 mV
and for cat brain, from Eccles JC. The Physiology of Nerve Cell, 1957, Johns Hopkins U Press, Baltimore.

$$\Delta E = -0.0617 \log \frac{[0.125 \text{ M } Cl^-]outside}{[0.009 \text{ M } Cl^-]inside}$$

$\Delta E = -0.0705$ V or -70.5 mV

3.b Redox Potential of Half Reactions

$$E_h = E^o + \frac{RT}{nF} \ln \frac{[oxidized]}{[reduced]}$$

where:
R ~ 8.31431 J/°K./mole
T ~ °K.
n ~ number of electrons
F ~ Faraday ~ 96,494 coulombs
ln ~ 2.303 $\log_{10}$

IV Eqn 4 Redox State Equations. [NAD+]/[NADH] or [NADP+]/[NADPH].

Near equilibrium reactions are given a number depending upon location. The $E^{o'}$ of the [NAD+]/[NADH] couple at pH 7 is -0.32 V. That of the [NADP+]/[NADPH] couple, -0.335 V.

Abbreviation Definition of K_{eq} Enzyme No.	Value of K_{eq} at pH = 0	Value of K_{eq} at pH 7	$E^{o'}$ at pH 7.0 $\frac{\text{oxidized}}{\text{reduced}}$ V	$E^{o'}$ at pH 7.0 CO_2 = 1.5 mM or 0.5 mM NH_4^+ or 1 mM Pi V
Cytoplasmic NAD - Linked Dehydrogenases				
4C1 $K_{LDH} = \frac{[pyruvate^-][NADH][H^+]}{[l\text{-lactate}^-][NAD^+]}$ EC 1.1.1.27	1.11×10^{-11} M	1.11×10^{-4}	-0.201	

-continued

4C2	$K_{MDH} = \frac{[\text{oxaloacetate}^{2-}][NADH][H^+]}{[\text{l-malate}^{2-}][NAD^+]}$ EC 1.1.1.37	2.86×10^{-12}M	2.86×10^{-5}	−0.184	
4C3	$K_{GPDH} = \frac{[\alpha\text{-glycerol-P}^{2-}][NADH][H^+]}{[DHAP^{2-}][NAD^+]}$ EC 1.1.1.94	1.3×10^{-11}M	1.3×10^{-4}	−0.203	
4C4	$K_{GAPDH} = \frac{[1,3\ \text{DiPG}^{4-}][NADH][H^+]}{[GAP^{2-}][Pi^{2-}][NAD^+]}$ EC 1.2.1.12	5.3×10^{-8}M	5.3×10^{-1}	−0.302	−0.222 Here, Pi is a reactant
	$K_{ADH} = \frac{[\text{acetaldehyde}][NADH][H^+]}{[\text{ethanol}][NAD^+]}$ EC 1.1.1.1	1.94×10^{-11}M	1.9×10^{-4}	−0.209	
	$K_{IdDH} = \frac{[\text{d-fructose}][NADH][H^+]}{[\text{d-sorbitol}][NAD^+]}$ EC 1.1.1.14	1.14×10^{-9}M	1.14×10^{-2}	−0.262	
	Mitochondrial NAD - Linked Dehydrogenases				
4M1	$K_{HBDH} = \frac{[\text{acetoacetate}^-][NADH][H^+]}{[\text{d-B-hydroxybutyrate}^-][NAD^+]}$ EC 1.1.1.30	4.93×10^{-9}M	4.93×10^{-2}	−0.281	
4M2	$K_{GlDH} = \frac{[\alpha\text{-KG}^{2-}][NH_4^+][NADH][H^+]}{[\text{l-glutamate}][NAD^+]}$ EC 1.4.1.3	3.87×10^{-13}M^2	3.87×10^{-6}M	−0.158	−0.257
	$K_{AlDH} = \frac{[\text{acetate}^-][NADH][H^+]^2}{[\text{acetaldehyde}][NAD^+]}$ EC 1.2.1.3	1.45×10^{-5}M^2	$1.45 \times 10^{+9}$	−0.596	
	Cytoplasmic NADP - Linked Dehydrogenases				
4T1	$K_{IcDH} = \frac{[\alpha\text{-KG}^{2-}][CO_2][NADPH]}{[\text{l,r-isocitrate}^{3-}][NADP^+]}$ EC 1.1.1.42	1.17M	1.17M	−0.337	−0.422 Here, CO_2 is a reactant
4T2	$K_{Malic\ Enz} = \frac{[\text{pyruvate}^-][CO_2][NADPH]}{[\text{malate}^{2-}][NADP^+]}$ EC 1.1.1.40	3.44×10^{-2}M			
4T3	$K_{6PGDH} = \frac{[\text{ribulose 5-P}^{2-}][CO_2][NADPH]}{[\text{6-phosphogluconate}^{3-}][NADP^+]}$ EC 1.1.1.43	1.72×10^{-1}M			
	Linking Isomerases				
4L1	$K_{GOT} = \frac{[\alpha\text{-KG}^{2-}][\text{l-aspartate}^-]}{[\text{l-glutamate}^-][\text{oxaloacetate}^-]}$ EC 2.6.1.1	6.61			
4L2	$K_{GPT} = \frac{[\alpha\text{-KG}^{2-}][\text{l-alanine}]}{[\text{l-glutamate}^-][\text{pyruvate}^-]}$ EC 2.6.1.2	1.52			
4L3	$K_{TPI} = \frac{[\text{dihydroxyacetone-P}^{2-}]}{[\text{glyceraldehyde 3-P}^{2-}]}$ EC 5.3.1.1	22			

References for Values of Near-Equilibrium Reactions in Equation 4

Equation	Abbreviation	Reference
4C1	K_{LDH}	Williamson DH, Lund P, Krebs HA. Biochem J 103: 514–527, 1967
4C2	K_{MDH}	Guynn R, Gelberg H, Veech RL. J Biol Chem 248: 6957–6965, 1973
4C3	K_{GPDH}	Russman W. Thesis, Munich, 1969.
4C4	K_{GAPDH}	Cornell N, Leadbetter M, Veech RL. J Biol Chem 254: 6522–6527, 1979
4M1	K_{HBDH}	Williamson DH, Lund P, Krebs HA. Biochem J 103: 514–527, 1967
4M2	K_{GLDH}	Engel P, Dalziel K. Biochem J 105: 691–695, 1967
4T1	K_{IcDH}	Londesbourgh J, Dalziel K. Biochem J 110: 217–222, 1968
4T2	$K_{M.E.}$	Veech R, Eggleston LV, Krebs HA. Biochem J 115: 609–619, 1967

-continued

4T3	K_{6PGDH}	Villet R, Dalziel K. Biochem J 115: 633-638, 1969
4L1	K_{GOT}	Krebs HA. Adv Enz Reg 13: 449-472, 1975
4L2	K_{GPT}	Krebs HA. Adv Enz Reg 13: 449-472, 1975
4L3	K_{TPI}	Veech RL, Raijman L, Dalziel K, Krebs HA. Biochem J 115: 837-842, 1969

*The enzyme aldose reductase EC 1.1.1.21 may be redox active during fructose infusion in certain tissues. The reaction is:

$$K_{Aldose\ R} = \frac{[\text{d-sorbitol}][NADPH][H^+]}{[\text{d-glucose}][NADP^+]} \sim 2 \times 10^{-11}\ \text{M.}^*\ \text{My estimate}$$

For description, see Hayman S, Kinoshita JH. J Biol Chem 240: 877, 1965

V Eqn 5 Phosphorylation State Equations - $[\Sigma ATP]/[\Sigma ADP][\Sigma Pi]$
Veech RL, Lawson JR, Cornell NW, Krebs HA. J Biol Chem 254: 6538-6547, 1979

5a. The equilibrium constant of the glyceraldehyde 3-phosphate dehydrogenase (EC 1.1.1.29) and 3 phosphoglycerate kinase reactions (EC 2.7.2.3) at 38° C., I = 0.25, and free $[Mg^{2+}]$ = 1 mM is:

$$K_{G+G} = \frac{[\Sigma 3PG]}{[\Sigma GAP]} \cdot \frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]} \cdot \frac{[NADH][H^+]}{[NAD^+]} = 1.83 \times 10^{-4}$$

5b. Combining the above reaction with K_{LDH} and substituting [DHAP] = [GAP]/22

$$\frac{K_{G+G}}{K_{LDH}} = \frac{[\Sigma 3PG]}{[\Sigma GAP]} \cdot \frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]} \cdot \frac{[\text{l-lactate}]}{[\text{pyruvate}]} = 1.65 \times 10^{+7} M^{-1}$$

5c. Or:

$$\text{Free Cytoplasmic } \frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]} = \frac{[\Sigma DHAP]}{[\Sigma 3PG]} \cdot \frac{[\text{pyruvate}]}{[\text{l-lactate}]} \times 7.5 \times 10^{+5} M^{-1}$$

5d. Alternatively, from the creatine phosphokinase reaction (EC 2.7.3.2)

$$K_{CK} = \frac{[\Sigma ATP]}{[\Sigma ADP]} \cdot \frac{[\text{creatine}]}{[\Sigma\text{creatine-P}][H^+]} = 1.66 \times 10^{-9} M^{-1}$$

For the Pyrophosphorylation State or [PPi]/[Pi]:
Lawson JWR, Guynn RW, Cornell NW, Veech RL. In Gluconeogenisis (Hanson RW, Mehlman MA eds) pp 481-511, John Wiley, New York, 1976

5e. From the UDPG Pyrophosphorylase reaction (EC 2.7.7.9):

$$\text{Free Cytoplasmic [PPi]} = \frac{[\Sigma\text{glucose 1-P}][\Sigma UTP]}{[\Sigma\text{UDPglucose}]' K_{UDPGPPiase}}$$

where $K_{UDPGPPiase} = 4.55$

5f. For liver and blood glucose:

$$K_{G\text{-}PPi\ Trans\ Pase} = \frac{[\Sigma\ \text{Glucose 6-P}][\Sigma Pi]}{[\text{Glucose}][\Sigma PPi]} = 45.9$$

5g. $$K_{G6\text{-}P\text{-}PPi\ Trans\ Pase} = \frac{[\text{free F 1,6 diP}][\Sigma Pi]}{[\Sigma\text{fructose 6-P}][\Sigma PPi]} = 29.0$$

VI Eqn 6 Determination of Osmotic Pressure - π
Van't Hoff JH. Arch Neerl Sci 20: 239-303, 1886

$$\pi = \Sigma[C]\,RT$$

where:
$\pi \sim$ osmotic pressure in atmospheres (relative to pure H_2O)

-continued

$\Sigma[C] \sim$ [concentrations] of solutes in mole/liter
$R \sim$ gas constant = 0.082 liter atmospheres/mole/degree K
$T \sim 273 + °C$.

VII Eqn 7 The Equation of State of the Cell
Relating the E across the cell membrane, the distribution of $[Na^+]$, $[K^+]$, $[Cl^-]$, and $[Ca^{2+}]$ between extracellular fluid and cytoplasmic H_2O and hence cell volume to the cytoplasmic [ATP]/[ADP][Pi]

$$\Delta G_{Na/K\ ATPase} = \Delta G^o_{ATPase} + \Delta G^o_{ions} + RT \ln \frac{[\Sigma ADP][\Sigma Pi]}{[\Sigma ATP]} + RT \ln \frac{[Na^+]_o^3[K^+]_i^2[Cl^-]_o}{[Na^+]_i^3[K^+]_o^2[Cl^-]_i} + T\Delta S$$

Since $\Delta G = 0$, then:
$0 = -7.73$ kcal/mole + 0 + (−6.3 kcal/mole) + 8.5 kcal/mole + 5.5 kcal/mole

$$\text{As 1 kcal/mole} = \frac{0.082\ \text{liter atmos/mole/°K.}}{1.98 \times 10^{-3}\ \text{kcal/mole/°K.}} \times \frac{1}{22.4\ \text{l/mole}} = 1.85\ \text{atmospheres}$$

then the TS term = 5.5 × 1.85 = 10.2 atmospheres.
And further from Van't Hoff (Eqn 6)

$$\Sigma[C]_{in} - \Sigma[C]_{out} = \frac{\pi}{RT}$$

$\Sigma[C]_{in} - \Sigma[C]_{out} = 0.40$ moles/L

Eqn 7 states that since uT H_2O outside = uT H_2O inside, the cell is prevented from swelling by the Na^+/K^+ ATPase which electroneutrally pumps out 2 mOsmoles/ATP hydrolysed. The ΔE across the cell (membrane) is reflected by the distribution of $[Cl^-]_o/[Cl^-]_i$ in accordance with the Nernst equation (Eqn 3). The $T\Delta S$ or decreased entropy within the living cell represents the increase "order" characteristic of the living cell. See Eqn 0.

7b. From the high capacity Na^+/Ca^{2+} exchanger written in an electroneutral manner reflecting the free permeability of Cl^- in accordance with the dictates of the Nernst equation, (Eqn 3):

$$3Na^+_o + Ca^{2+}_i + Cl^-_o \longleftrightarrow 3Na^+_i + Ca^{2+}_o + Cl^-_i$$

The net osmolar movement of eqn 7a is 2 osmoles ⟶ outside.
In contrast, the net movement of eqn 7b is 3 osmoles ⟶ inside, requiring the Na^+/K^+ ATPase to cycle 3 times for each 2 times the Na^+/Ca^{2+} exchange mechanism operates in order to maintain osmotic equilibrium.
The gradient $[Ca^{2+}]_i/[Ca^{2+}]_o$ is thus a direct function of the $[Na^+]_o^3/[Na^+]_i^3$, (the $[Cl^-]_o/[Cl^-]_i$), and a function of the phosphorylation and entropy state of the cell.

It will be clear to those skilled in the art that equation 7 is the statement of the reaction which links the external environment of the cell to its internal environment

and metabolic machinery. Extracellular fluid is thus a creation of the metabolic process of the cell. Changing the external [Na^+], [K^+], [Cl^-], or [Ca^{2+}], or the [H_2O] must necessarily effect the same parameters inside the cell.

Additionally, the redox and phosphorylation states, the ΔE, and the $T\Delta S$ of the cell are all related and therefore manipulable by the relationships given.

To control these parameters one needs to use solutions as provided herein which include defined concentrations of Na^+, K^+, Cl^-, and Ca^{++} and the related ions HCO_3^-, H^+, at a defined Mg^{2+} concentration and with a defined osmotic pressure.

Thus, the present invention provides a process for regulating:

(1) Distribution of water between intracellular and extracellular fluid.

(2) Distribution of the inorganic electrolytes Na, K, Cl and Ca between intracellular and extracellular fluid.

(3) and transmembrane cellular potential

This process is practiced by contacting cells with aqueous near-equilibrium couples as taught by this inventor or by varying the external concentration of Na^+, K^+, Cl^- or Ca^{2+}. For example a solution with low Na:Cl ratio raises the phosphorylation potential (See Table III above). In other circumstances, raising Na:Cl outside may raise cellular [Ca^{2+}] for example in rat liver.

Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

I claim:

1. An aqueous solution suitable for fluid therapy comprising on the basis of 1 liter of solution about 130 to 165 mM sodium, about 80 to 130 mM chloride, and about 0.5 to 60 mM at least one of the following:

(a) l-lactate and pyruvate, the l-lactate to pyruvate ratio being about 20:1 to 1:1,

(b) d-beta hydroxybutyrate and acetoacetate, the d-beta hydroxybutyrate to acetoacetate ratio being about 6:1 to 0.5:1, the sodium to chloride ratio being about 1.24 to 1.6, and the pH ranging from about 5 to 9.

2. A solution in accordance with claim 1 containing from about 0.5 to 5 mM calcium.

3. A solution in accordance with claim 1 containing from about 0.5 to 3 mM magnesium.

4. A solution in accordance with claim 1 containing from about 0.5 to 10 mM potassium.

5. A solution in accordance with claim 1 containing from 0 to about 300 mM glucose.

6. A solution in accordance with claim 1 containing from about 0.5 to 60 mM of bicarbonate and carbon dioxide, the bicarbonate to carbon dioxide ratio being about 0.1:1 to 55:0.1.

7. An electrolyte solution suitable for dilution and for resuscitation therapy comprising on the basis of 1 liter of solution 160 to 2400 mM sodium and sufficient mM chloride to produce a sodium to chloride ratio from about 1.24 to 1.6, and from about 80 to 465 mM of at least one of the following:

(a) l-lactate and pyruvate, the l-lactate to pyruvate ratio being about 20:1 to 1:1,

(b) d-beta hydroxybutyrate and acetoacetate, the d-beta-hydroxybutyrate to acetoacetate ratio being about 6:1 to 0.5:1,

the pH being about 5 to 9.

8. The solution of claim 7 which has been diluted with an aqueous dextrose solution to produce a product solution containing less than about 130 mM sodium.

9. An in vivo process for maintaining normal cellular free [NAD^+]/[NADH] ratios and phosphorylation states which comprises introducing parenterally into a living mammal a physiologically effective amount an aqueous solution comprising on the basis of 1 liter of solution about 130 to 165 mM sodium, about 80 to 130 mM chloride, and about 0.5 to 80 mM of at least one of the following:

(a) l-lactate and pyruvate, the l-lactate to pyruvate ratio being about 20:1 to 1:1,

(b) d-beta hydroxybutyrate and acetoacetate, the d-betahydroxybutyrate to acetoacetate ratio being about 6:1 to 0.5:1,

the sodium to chloride ratio being about 1.24 to 1.6, and the pH ranging from about 5 to 9.

10. The process of claim 9 wherein said solution additionally contains from 0 to about 300 mM glucose.

11. The process of claim 9 wherein said solution additionally contains about 10 to 60 mM bicarbonate and carbon dioxide, the bicarbonate to carbon dioxide ratio being about 0.1:1 to 55:0.1 and wherein the free cytosolic [$NADP^+$]/[NADPH] ratios are also maintained.

12. In a process where renal function of a living mammal is replaced by dialysis and wherein the dialysis fluid contains dissolved therein from about 130 to 165 mM sodium, and also from about 81 to 130 mM chloride, and said fluid has a sodium to chloride ratio ranging from about 1.24 to 1.6, a pH from about 5 to 9, and a milliosmolarity from about 260 to 800, the improvement which comprises including in said dialysis fluid from about 25 to 455 mM of at least one of the following substance pairs in the respective concentrations indicated:

from about 0 to 55 mM bicarbonate and carbon dioxide, the bicarbonate to carbon dioxide ratio being 0.1:1 to 55:0.1,

from about 0 to 55 mM of l-lactate and pyruvate, the l-lactate to pyruvate ratio being 20:1 to 1:1, and

from about 0 to 55 mM of d-betahydroxybutyrate and acetoacetate, the d-betahydroxybutyrate to acetoacetate ratio being 6:1 to 0.5:1.

13. The process of claim 8 wherein said solution additionally contains from 0 to about 45 mM bicarbonate.

14. The process of claim 13 wherein said pH of said solution is achieved by admixture of said bicarbonate to said carboxylic acid and wherein the final concentrations thereof are such as to produce a pH in said solution which satisfies the relationship:

$$pH = pK_{a'} - \log\left(\frac{[HCO_3^-]}{2([HCO_3^-] - [HA])} - \frac{1}{2}\right)$$

wherein:

$pK_{a'}$ is defined as the apparent dissociation constant of carbonic acid under physiological conditions at physiological temperature and ionic strength and is taken to be 6.1,

$[HCO_3^-]$ is the concentration of bicarbonate present in said solution,

[HA] is the concentration of said carboxylic acid, and

pH is conventionally defined as the negative logarithm to the base ten of the hydrogen ion concentration of the resulting said solution.

15. The process of claim 13 wherein said carbon dioxide is produced in situ by including in said solution a dissolved mixture of

(A) at least one member of the group consisting of physiologically acceptable bicarbonate salts, and

(B) at least one carboxylic acid selected from the group consisting of l-lactic acid, pyruvic acid, d-betahydroxybutyric acid, and acetoacetic acid,

and provided that:

(a) the total molar quantity of said carboxylic acid and the total molar quantity of said bicarbonate salts is such that there is produced in said solution a quantity of dissolved carbon dioxide sufficient to make said mole ratio of said bicarbonate anions to said carbon dioxide fall in within said range, and

(b) the total quantity of all bicarbonate anions remains within a value such that said mole ratio of said bicarbonate anions in said solution to said carbon dioxide falls within said range, and

(c) the total individual quantities of said respective carboxylic acids is such that said mole ratio of l-lactate to pyruvate, and said mole ratio of d-betahydroxybutyrate to acetoacetate each remain within said respective ranges.

* * * * *

US006020007A

United States Patent [19]

Veech

[11] Patent Number: 6,020,007

[45] Date of Patent: Feb. 1, 2000

[54] **FLUID THERAPY WITH L-LACTATE AND/OR PYRUVATE ANIONS**

[75] Inventor: **Richard L. Veech**, Rockville, Md.

[73] Assignee: **BTG International Limited**, London, United Kingdom

[21] Appl. No.: **08/179,880**

[22] Filed: **Jan. 11, 1994**

Related U.S. Application Data

[60] Continuation of application No. 07/846,081, Mar. 5, 1992, abandoned, which is a division of application No. 06/940,333, Dec. 17, 1986, Pat. No. 5,100,677, which is a continuation-in-part of application No. 06/810,918, Dec. 18, 1985, abandoned, which is a continuation-in-part of application No. 06/748,232, Jun. 24, 1985, Pat. No. 4,663,166, which is a continuation-in-part of application No. 06/623,102, Jun. 22, 1984, abandoned.

[51] **Int. Cl.**[7] **A61K 33/14**; A61K 33/02; A61K 31/215; A61K 31/22

[52] **U.S. Cl.** **424/677**; 424/678; 424/679; 424/680; 424/681; 424/719; 514/529; 514/546; 514/557; 514/561; 514/572

[58] **Field of Search** 424/677, 678, 424/679, 680, 681, 719; 514/557, 578, 529, 561, 546

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,067,999	1/1978	Glabe et al.	424/317
4,351,835	9/1982	Stanko	424/252
4,363,815	12/1982	Yu et al.	424/274
4,579,955	4/1986	Lammerant et al. .	
4,663,166	5/1987	Veech	514/23
4,771,074	9/1988	Lammerant et al. .	
5,100,677	3/1992	Veech	424/681

FOREIGN PATENT DOCUMENTS

108820	11/1982	European Pat. Off. .
161472	11/1985	European Pat. Off. .

OTHER PUBLICATIONS

P.L. Kirkendol et al., vol. XXIII Trans. Am. Soc. Artif. Intern. Organs (1977) pp. 399–405.

Martindales Extra Pharmacopoeia, 28th edition (1982) pp. 634, 637, 638, 640 and 641.

The Journal of Biological Chemistry, vol. 259, No. 1, pp. 231–236, Jan. 10, 1984, The Metabolism of Acetone in Rat, Casazza, et al.

The New England Journal of Medicine, vol. 306, No. 22, pp. 1344–1348, Jun. 3, 1982, D–Lactic Acidosis Due to Abnormal Gut Flora, Stolberg, et al.

The New England Journal of Medicine, vol. 301, No. 5, pp. 249–251, Aug. 2, 1979, D–Lactic Acidosis in a Man With the Short–Bowel Syndrome, Oh, et al.

The Journal of Pediatrics, vol. 102, No. 2, pp. 234–238, Feb. 1983, D–Lactic Acidosis in Children: An Unusual Metabolic Complication of Small Bowel Resection, Perlmutter, et al.

Fresenius–Infusionstherapie (1983) S. 211.

DAB S 712 713 Anlage III + Rostffzert (1968).

Jap. J. Artificial Organs 12 (1983) S 878–882.

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[57] **ABSTRACT**

Electrolyte solutions are provided which are useful in electrolyte and fluid therapy, parenteral nutrition and dialysis. The Na:Cl ratio is normalized, plasma and cellular pH are normalized and cellular cofactor ratios are normalized in a manner which decreases toxicity over prior art solutions.

30 Claims, No Drawings

FLUID THERAPY WITH L-LACTATE AND/OR PYRUVATE ANIONS

RELATED APPLICATION

This is a continuation of application Ser. No. 07/846,081, filed Mar. 5, 1992 now abandoned which is a division of Ser. No. 06/940,333 filed Dec. 17, 1986, now U.S. Pat. No. 5,100,677 which is a continuation-in-part of my U.S. patent application Ser. No. 06/810,918, filed Dec. 18, 1985, now abandoned which in turn is a continuation-in-part of my U.S. patent application Ser. No. 06/748,232, filed Jun. 24, 1985, now U.S. Pat. No. 4,663,166, which in turn is a continuation-in-part of U.S. patent application Ser. No. 06/623,102 filed Jun. 22, 1984, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention lies in the field of fluid therapy in humans, and more particularly in the field of aqueous solutions for parenteral, oral, dialysis, and irrigation therapy which employ at least one of l-lactate anions, pyruvate anions, d-betahydroxybutyrate anions, acetoacetate anions, or mixtures thereof in combination with selected cations.

2. Prior Art

Previously, I have provided improved electrolyte solutions for in vivo and in vitro usage which contain l-lactate and pyruvate anions, and/or d-betahydroxybutyrate and acetoacetate anions in respective defined ratios in combination with defined Na:Cl ratios; see my copending U.S. patent applications Ser. Nos. 748,232 and 747,792, both filed Jun. 24, 1985, and also my copending U.S. patent application Ser. Nos. 747,858 and 748,184, also filed on such date. However, it is now appreciated that the benefits of using l-lactate, pyruvate, d-betahydroxybutyrate, and/or acetoacetate anions need not be restricted by these previously taught relationships of anion pair ratios to Na:Cl ratios.

The prior art indicated in the "Background" sections of these earlier patent applications is incorporated by reference into the present application.

Previously, only racemic mixtures of lactate anions containing both d- and l-forms of lactate have been used in aqueous solutions for human parenteral therapy. The other major organic anion used in human parenteral fluids has been acetate. So far as is now known, the natural l-form of lactate anion has heretofore never been used, apart from the unnatural d-form, in human fluid therapy.

Sodium lactate solutions, used in pharmaceutical practices, are not specified in terms of isomeric structure. In the U.S. and British Pharmacopeias, lactate is defined and approval was duly granted for use of the d,l-lactate mixture. Hence, the d,l-lactate is the form used in contemporary pharmaceutical practice. The l-lactate is recognized to be the physiologically predominant form which is metabolized by different pathways and with different effects than is the d-lactate.

The toxicity of d-lactate has been described in humans (see Oh M S et al *N Eng J Med* 301: 249–251, 1979; Perlmutter, D H et al *J Pediatrics* 102: 234–238, 1983; Stolberg, L et al *N Eng J Med* 306: 1344–1348, 1982). Thus, the d-form has now been discovered to cause adverse and toxic effects when administered to mammals. For example, when an aqueous 20 mM/l d-lactate (or d-lactic acid) is administered parenterally to a rat, swelling of brain tissue is observed because the brain takes in the slowly metabolized d-lactate$^-$ plus an equivalent amount of K^+. With continued

administration, coma develops, the cerebral edema worsens and death ensues. In contrast, when l-lactate is similarly administered, the differential concentration of l-lactate between intracellular and extracellular fluid does not cause coma or death. For another example, Veech et al. (Veech, R L and Fowler, R C., "Cerebral Dysfunction and Respiratory Alkalosis During Peritoneal Dialysis with d-Lactate Containing Peritoneal Dialysis Fluids". Am. J. Med., 1987 (in press)) points out that the severe recurrent metabolic alkelemia described by Kenamond et al. ("Severe Recurrent Alkalemia in a Patient Undergoing Continuous Cyclic Peritoneal Dialysis". Am. J. Med., 548–550, 1986) was secondary to an encephalopathy caused by the inclusion of d,l-lactate in routine dialysis fluids. Because of such encephalopathological results, parenteral solutions containing the racemic d,l-lactate anions should not be administered for therapeutic purposes.

All previous commercial formulations of fluids for human therapy use lactate or lactic acid in the racemic d,l form as defined in the United States or British Pharmacopeia (see the United States Pharmacopeia 21st edition, January 1985, p 581, 945–946, 1186; United States Pharmacopeia Convention, Rockville, and British Pharmacopeia 1980, p 250, 666, 667, Her Majesty's Stationary Office, London). Sodium d,l-lactate solutions are currently and conventionally used for three major purposes in current medical practice. First, sodium d,l-lactate solution is used parenterally as an alkalinizing agent to correct acidosis. Secondly, it is used in parenteral fluid therapy to normalize the Na:Cl ratio from the 1:1 ratio found in normal saline. Thirdly, it is used as the counter ion in peritoneal dialysis solutions. In addition, it could also be used in current hemodialysis to replace the acetate anion, or, in its H^+ form, as an acid to be added to a bicarbonate hemodialysis fluid.

Prior to the teachings contained in my afore referenced U.S. Ser. No. 748,232, pyruvate anions d-betahydroxybutyrate anions, and acetoacetate anions in aqueous solution, so far as is now known, were never used in human therapeutic fluids.

BRIEF SUMMARY OF THE INVENTION

This invention relates to a process for accomplishing fluid therapy without encephalopathy or metabolic bone disease and other complications resulting from use of present fluid formulations in a living human involving the introduction into the body of such human an aqueous solution containing at least one permeant monoanionic metabolite selected from the group consisting of l-lactate anions, pyruvate anions, d-betahydroxybutyrate anions, acetoacetate anions, or mixtures of such anions.

Here, l-lactate is defined as that form of lactate anion found in mammalian tissues and designated l or L-lactate. It is identified by its ability to react with NAD^+ to form pyruvate in a reaction catalyzed by mammalian lactate dehydrogenase (EC 1.1.1.27). The form of l-lactate which is dextrorotatory in aqueous solution is designated l-(+) while the salts of l-lactate which in aqueous solution are levorotatory are designated l-(-)lactate (see US Dispensatory. Osol, A, Pratt, R, Gennar, A R, eds. p 658. J R Lippcott. Philadelphia, 1973). Pyruvate and acetoacetate have no sterospecificity.

More particularly, this invention is directed to improved methods and optionally stable fluids for conventional administration to humans such as, (a) oral ingestion of an aqueous solution containing at least one of such anions, or a mixture of such anions, (b) parenteral therapy involving,

for example, the intravenous administration of an aqueous solution containing at least one of such anions, or a mixture thereof, (c) dialysis therapy (hemo or peritoneal) using aqueous solutions containing at least one of such anions, (d) dialysis therapy (hemo or peritoneal) where acetic acid is replaced with at least one acid of the group consisting of l-lactate, pyruvate, d-betahydroxybutyrate or acetoacetic acid, preferably l-lactate, and/or (e) irrigation therapy.

One presently preferred such anion comprises l-lactate. Thus, surprisingly, encephalopathy, metabolic bone disease, and many other complications are not only completely avoided by using l-lactate (or one of the other metabolite anions herein identified and used in the practice of this invention) in place of racemic d-l-lactate, but also the substitution of, for example, l-lactate for d-l-lactate, in solutions employed in fluid therapy, does not cause any change in the heretofore known beneficial physiological or pharmacological effectiveness of such fluids.

In general, a solution containing at least one such anion is administerable for generally the same purposes that prior art parenteral fluids or dialysis fluids are used which contain racemic d-l-lactate anions. For examples, such a solution can be used to treat acidosis, dehydration, blood electrolyte depletion, shock, malnutrition, uremia and the like.

Because mixtures of l-lactate anions and pyruvate anions, and mixtures of d-betahydroxybutyrate anions and acetoacetate anions, in solutions each constitute near-equilibrium couples, which can vary widely in concentration under normal physiological conditions, as explained, for example, in my aforereferenced U.S. patent application Ser. No. 748,232, these anions can be employed with little or no adverse side effects in parenteral fluids and the like. Moreover, the therapeutic use of these anion couples (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions, (b) thus tends to prevent hyperchloremic acidosis, and (c) accomplishes electrolyte and fluid and resuscitation therapy. The anions taught by this invention permit one to avoid the known untoward effects of high levels of the d-lactate anion (see Veech, R L, Fowler, R C, op. cited above) or of acetate anion which are now the major organic anions conventionally added to parenteral fluids (See Veech R L. The toxic impact of parenteral solutions on the metabolism of cells: a hypothesis for physiological parenteral therapy. Am J Clin Nutr 44: 519–551, 1986).

Other and further objects, aims, purposes, features, advantages, embodiments, applications, and the like will be apparent to those skilled in the art from the teachings of the present specification taken together with the claims.

DETAILED DESCRIPTION

For the fluid therapy purposes of my present invention, any conventional administration procedure is suitable, although parenteral (particularly intravenous) administration during hemo or peritoneal dialysis is presently preferred.

For example, sodium l-lactate aqueous solutions, which are stable and easily sterilized, can be used in infusion fluids in place of sodium bicarbonate for treatment for acidosis. For example, the bicarbonate may be dissolved immediately before use in the infusion fluid by light agitation and preferably warmed to body temperature. In such a replacement, 1 g sodium bicarbonate corresponds to about 1.33 g sodium l-lactate, and 1 g sodium l-lactate corresponds to about 0.75 g sodium bicarbonate. The bicarbonate or l-lactate solutions are preferrably administered diluted with glucose solution or distilled water. The alkalizing action of sodium l-lactate is diminished in severe liver damage since its breakdown is retarded. See, for example, Documenta Geigy 6th ed, pp. 331–332, Geigy, Manchester, 1962.

In practice, the calculation of the quantity of an alkalizing infusion solution required for adults is based on an average value for the water content of the body of 50% by weight and on a uniform intra- and extra-cellular distribution of bicarbonate, l-lactate, d-betahydroxybutyrate, and other aforementioned permeant monovalent anionic metabolites. This method naturally yields only rough figures. The calculation can be simplified by reckoning in milliequivalents desired change in the alkali reserve. For example, in order to increase or decrease the alkali reserve in a patient weighing 70 kg by 5 mEq, a quantity of, for example, l-lactate, bicarbonate or d-betahydroxybutyrate anions of 70×6×0.5= 210 mEq must be administered. In order to avoid the danger of an acidosis becoming converted into an alkalosis, it is advisable not to attempt a complete normalization of the alkali reserve by means of an alkalizing solution, and such solutions should never be administered without supplementary potassium.

In children, a higher water content of about 66% must be reckoned with, so that the calculation yields relatively high infusion quantities. The differences between the calculated and observed effects of alkalizing and of acidifying compounds can be considerable since the above approximate calculation ignores a number of important factors.

In diabetic acidosis, many authors consider it is inadvisable to administer large quantities of sodium salts without potassium salts. On the other hand, extremely good results have been reported in the intensive lactate treatment of diabetic coma. There is no doubt that a moderate alkali therapy with l-lactate and/or pyruvate is indicated in diabetic ketosis with very much lowered alkali reserve, since it has been shown that insulin activity is inhibited by acidosis and that acidosis increases the blood sugar. Clearly use of d-betahydroxybutyrate or acetoacetate would not be suitable for use in diabetic ketoacidosis. As those skilled in the art will also appreciate, the ketone bodies would not be appropriate for use in pregnant women.

When using solutions such as "Lactated Ringer's" (see, for example, my aforereferenced U.S. Ser. No. 748,232) to replete body water and electrolytes, the 28 mM d,l-lactate of the prior art is replaced with, for example, 28 mM l-lactate. In this way, the Na:Cl ratio, in such an l-lactate solution, is moved, if desired, towards a normal ratio of 1.36 as found in normal human plasma. Thus, hyperchloremic acidosis resulting from large infusions of normal sodium chloride solutions is avoided. The same considerations apply to use of such solutions in dialysis (see, for example, my aforereferenced U.S. patent applications Ser. Nos. 748,232 and 748,184).

Alternatively, in all the present new solutions, d-betahydroxybutyrate anions, for example, can be used alternatively in place of l-lactate anions. Additional benefits may accrue from the use alternate or combined use of pyruvate and acetoacetate.

A preferred application for this invention involves usage of a mixture of anions of l-lactate and pyruvate, or a mixture of anions d-betahydroxybutyrate and acetoacetate, as indicated, in solutions. Under special circumstances, use of one or the other of such anions alone may be preferred, such as in cases of severe reduction of the pyridine nucleotide systems where administration of pyruvate anions may be preferred. In conditions where long stability of mixed aque-

ous solutions presents a practical problem, use of l-lactate or d-betahydroxybutyrate alone confers stability on the solution and is to be preferred over the currently used d,l-lactate or acetate.

For one example, to correct an acidosis wherein a 70 kg man is 6 mEq below the normal plasma bicarbonate level of 26–30 mEq/L, then 70×6×0.5 or 210 mEq is infused with a fluid of this invention containing bicarbonate anions and l-lactate anions as described hereinbelow, over a 2 to 4 hour period. Other dosages and rates of infusion may be used, if desired, depending on the clinical situation.

For a second example, a liter of solution of the composition of the current Ringer's lactate (for the composition thereof, see my aforereferenced U.S. Ser. No. 748,232) may be infused over a four hour period into a dehydrated 70 kg man with the exception that the d,l-lactate used is replaced with l-lactate.

For a third example, the prior art accomplishment of peritoneal dialysis by infusion into the peritoneum of 2 L of a conventional d,l-lactate based or acetate based peritoneal dialysis solution, is changed in that the 35–45 mM d,l-lactate or acetate is altered and replaced by 35–45 mM l-lactate. After remaining in the peritoneum for about ½ hour, the fluid is drained off and the process repeated until the blood urea nitrogen (BUN) is decreased to the level desired.

In parenteral therapy, the total concentration of anions selected from the above indicated anion group, a present preference being l-lactate, pyruvate, and/or mixtures thereof, can range from about 0.01 to 2400 millimoles per liter, though larger and smaller quantities can be used depending upon circumstances. The rate of introduction into a human patient, and the dosage used, are generally the same as are conventionally used in solutions containing, for example, d,l-lactate.

A present preference is to employ, for fluid therapy, an aqueous solution wherein the total concentration of l-lactate or pyruvate anions ranges from about 1 Molar to 1 millimolar. In a more preferred form, from about 28 to 45 millimoles (total) of such anions are present (such as in an improved Ringer's lactate or in improved peritoneal dialysis fluids).

Although a solution taught by the present invention may contain either l-lactate or pyruvate alone, as essentially the sole organic metabolic anion, a mixture of l-lactate anions and pyruvate anions may also be used, and similarly a mixture of d-betahydroxybutyrate anions and acetoacetate anions may be used. When such an anion redox couple is employed, it is presently preferred to employ a milliequivalent ratio of l-lactate anions to pyruvate anions in the range from about 20:1 to 1:1, and a milliequivalent ratio of d-betahydroxybutyrate anions to acetoacetate anions in the range from about 6:1 to 0.5:1.

The l-lactic, pyruvic, d-betahydroxybutyric, and acetoacetic acids themselves as such, may be used. For example, such can be used in combination with aqueous bicarbonate anions; for instance, in sodium bicarbonate containing solutions. Also, one can employ, in the starting solutions used in the processes of present invention, aqueous solutions which contain, along with such metabolite anions as taught in this invention, at least one cation selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium. Preferably, from about 0.01 to 2400 millimoles per liter of such anions are present.

Inorganic physiologically acceptable anions, besides bicarbonate, may also be present, such as chloride, phosphate, and sulfate, if desired, and if such are present, the respective quantities present are preferably similar to corresponding physiologic levels. A difference between the total milliequivalents of the cations present in a solution and the total milliequivalents of the organic anions of the specified group employed in the practice of this invention (l-lactate, pyruvate, d-betahydroxybutyrate, and acetoacetate) can be provided by other physiologically acceptable anions.

It is considered to be physiologically advantageous and it is generally preferred in the practice of this invention, to maintain the levels of the respective organic metabolite anions employed at values which are approximately physiologic. Also, when a mixture of the monocarboxylic metabolic anions is employed in a given solution, it is not necessary to employ redox couple anion pairs since this use of these defined monocarboxylic metabolite anions does not produce the toxic effects resulting from the present use of d,l-lactate or acetate. Further, it appears to be desirable to employ such anionic metabolites in combination with bicarbonate anions in conditions where large volumes of fluid are to be used and administration of calories is not desired, such as in peritoneal dialysis.

Additionally and preferably, such a solution may contain dissolved therein at least one osmotically active, substantially nonionic substance in accord with, for example, teachings for prior art d,l-lactate and acetate containing solutions. Examples of suitable such nonionic substances include glucose (preferred), fructose, glycerol, sorbitol, and the like. Typically, and preferably, such a solution has an osmolarity ranging from about 240 to 2400 mOsmoles/liter.

In addition, formulations containing ionic nutrients, such as l-amino acids, can benefit from the addition of at least one of the metabolite monocarboxylic acid anions taught herein. For example, the acetate anions present in current commercial amino acid formulations (which lead to metabolic bone disease) can be replaced by such anions. See, for example, my copending U.S. patent application Ser. No. 810,916, filed Dec. 18, 1985, and its continuation-in-part application filed on even date herewith, all the teachings of which are entirely incorporated hereinto by reference.

Also preferably, a starting solution used in the practice of this invention has a pH in the range from about 5 to 9, although for the contemplated human usage, a most preferred pH is about 7.4.

Additional cations and anions may be present in a starting solution as taught, for example, in my aforereferenced U.S. Ser. No. 748,232.

Thus, and as indicated above, such a solution can additionally contain bicarbonate anions. The pH of the resulting solution is adjustable to a desired value, such as a preferred value in the range from about 6 to 8.4, by the addition of the hydrogen form of at least one acid selected from the group consisting of l-lactic, d-betahydroxybutyric, acetoacetic, and pyruvic in an amount sufficient to give such desired value. For example, when an anion of an acid such as l-lactic acid, pyruvate acid, d-betahydroxybutyrate acid, or acetoacetic acid is to be added to a bicarbonate containing starting solution, a desired pH of such solution for use in human hemodialysis, or the like, is given by following the formula:

$$pH = pK_{a'} - \log\frac{[HCO_3^-]}{2([HCO_3^-] - [HA])} - \frac{1}{2}$$

where:

HA is the concentration of carboxylic acid in moles/liter, pK_a=6.10 at 38° C. (see Hastings, A B, et al., J. Biol. Chem. 79: 183–192, 1928).

In preferred applications of this sort, such as applications which can incorporate from about 28 to 40 mM/l HCO_3^-, about 2 to 9 mM/l l-lactic, pyruvic, d-betahydroxybutyric acid and/or acetoacetatic acid may generally be added. Such solutions are presently preferred for peritoneal or hemodialysis over existing fluids containing acetic acid or d,l-lactate because of the toxicity of the presently used acids.

Optionally, carbon dioxide may additionally be dissolved in such a solution, for example, in a range such as taught in my aforereferenced U.S. Ser. No. 748,232.

For purposes of practicing the present invention, only when both l-lactate and pyruvate anions are present in a milliequivalent ratio of from about 20:1 to 1:1, and/or both d-betahydroxybutyrate and acetoacetate anions are present in a milliequivalent ratio of from about 6:1 to 0.5:1 are present in admixture in a starting solution, and only when both sodium cations and chloride anions are also present in such a starting solution, then the milliequivalent ratio of Na^+ cation to Cl^- anions is always preferably below 1.24 or above 1.6. Thus, the practice of the methods of this invention does not require, in any given starting solution, both members of a redox active, near-equilibrium monocarboxylic acid couple; either member can be used individually. Also, such practice does not require the use of a narrowly specified range of Na^+ to Cl^- milliequivalent ratios (when such inorganic ions are both present).

Thus, as taught herein, therapy (including correction of acidosis, dialysis and/or fluid, electrolyte or nutrient replacement, and the like) in accord with the present invention can be accomplished through the use of any one or more of various anions herein taught in a starting solution wherein the cations are selected from among hydrogen, sodium, potassium, calcium, magnesium, and ammonium.

However, in the practice of this invention, preferrably only one monoanionic permeant metabolite (l-lactate, pyruvate, d-betahydroxybutyrate, and acetoacetate) is present in a solution at any one time. Thus, improvement in existing parenteral fluids can be achieved by use of l-lactate alone rather than d,l-lactate as is currently used, for example, in ambulatory parential dialysis fluids. The use of l-lactate in conjunction with other inorganic anions, but in the absence of the unstable ketoacid pyruvate, results in a fluid which has as long a chemical stability as the currently used d,l-lactate, but avoids the toxic effects resulting from the inclusion of the unnatural d-isomer. Thus, for example, one class of solutions, which has characteristically long shelf life and stability, contains as anions only l-lactate anions and/or d-betahydroxybutyrate anions and is termed herein Class I for convenience. This class is particularly useful where long term fluid storage is desirable. Another class of solutions, for example, contains as anions only pyruvate anions and/or acetoacetate anions and is termed herein Class II for convenience. Another class of solutions, for example, contains as anions only a mixture of l-lactate anions and pyruvate anions, or only a mixture of d-betahydroxybutyrate anions and acetoacetate anions, which is useful when redox control is desired, and is termed herein Class III for convenience. Table I illustrates various embodiments of such exemplary classes.

TABLE I

		Range of Concentration in mMoles/Liter		
Item No.	Component	Class I	Class II	Class III
1	l-lactate or betahydroxy-butyrate	0.01–2400		
2	pyruvate or acetoacetate		0.01–2400	
3	l-lactate plus pyruvate and/or d-betahydroxy-butyrate and acetoacetate			0.01–2400
4	(cations)	10^{-5}–10^{-9}	10^{-5}–10^{-9}	10^{-5}–10^{-9}
	(hydrogen)	0–2400	0–2400	0–2400
	sodium	0–2400	0–2400	0–2400
	potassium	0–1200	0–1200	0–1200
	calcium	0–1200	0–1200	0–1200
	magnesium	0–1200	0–1200	0–1200
	ammonium	0–10	0–10	0–10

Table II describes four classes of physiologic permeant monoanionic metabolite solutions suitable for each of three major fields of application. The genus class is described in Type A solutions of Table II, where d,l-lactate was previously used, and such improved solutions are suitable for use in treatment of certain forms of metabolic acidosis. For oral or parenteral use in resuscitation or the treatment of acidosis or severe fluid loss in diarrhea, the milliosmolarity of the solutions can vary widely from about 240 mOsmoles/L to 4800 mOsmoles/L. Prior art hypertonic sodium chloride solutions or hypertonic Ringer's lactate solutions have been widely used in resuscitation; such solutions can be reformulated as Type A solutions of this invention. Type B solutions of Table II are suitable for rehydration, electrolyte replacement, and/or nutrition. Type C solutions of Table II, are suitable for use as peritoneal dialysis and hemodialysis fluids. Type D solutions can be regarded as being similar in use to Type C solutions, but such include the permeant monoanionic metabolites in their hydrogen form in solutions which contain bicarbonate so as to achieve a desired pH in a manner which avoids the current toxic effects of high levels of acetate or d,l-lactate. These class D solutions are particularly suitable for use where it is desirable to avoid high levels of monocarboxylic acids. By using normal metabolites, these new fluids improve the corresponding prior art fluids, such as Ringer's lactate, hemodialysis fluids, and the like. With appropriate dosage, these fluids are also suitable for oral ingestion, such as under conditions requiring therapy where close patient monitoring is not possible.

For example, one can accomplish treatment of metabolic acidosis or resuscitation with improved sodium l-lactate or other Type A solutions as described in Table II. For treatment of acidosis, initial parenteral administration followed by oral administration is often preferred.

For example, one can accomplish parenteral fluid therapy with improved l-lactated Ringer's-type solutions (Type B) using the present invention in a human patient suffering from fluid, electrolyte, and/or nutritional depletion. Such a fluid may optionally contain non-ionic dissolved nutrients, usually glucose, from 0 to 280 mmoles/liter.

For another example, one can accomplish dialysis fluid therapy with an improved dialysis solution (Type C) using the present invention in a living human patient. The conventional techniques of hemo- and peritoneal dialysis known to the prior art are employable with the improved fluids of this type. Thus, the renal function of a living human patient

is replaced at least in part by passing the blood of the patient over one face of a dialysis membrane while a dialysis fluid is passed over the opposite face of such membrane.

In hemodialysis, it is preferable to use a dialysis solution of Type D containing from about 20 to 55 mM/l of bicarbonate anions, such solution also contains a sufficient portion of anions of at least one of said l-lactate, pyruvate, d-betahydroxybutyrate, and/or acetoacetate anions which are derived from the addition to said solution of, respectively, at least one of l-lactic acid, pyruvic acid, d-betahydroxybutyric acid and/or acetoacetic acid in a total amount which is sufficient to produce a pH in the range from about 5.5 to 8.2, such solution also has a milliosmolarity of from about 250 to 310 mOs/l.

Similarly, when peritoneal dialysis is being practiced, a Type D solution containing bicarbonate can be used and the carboxylic metabolite acid material(s) as above described is/are (as the case may be) also present, but here in an amount sufficient to produce a pH ranging from about 5.5 to 7.5. The milliosmolarity ranges from about 280 to 550 mOs/l achieved by disolution in such solution of sufficient nonionic nutrients.

Type D solutions are also adapted for parenteral administration, and for such purposes, a suitable composition of Type D is similar to that above indicated for peritoneal dialysis.

It will be appreciated that the designation mM and mM/l are used herein in their conventional manner to designate millimoles per liter.

TABLE II

Preferred Solutions (New)
units in mMoles/Liter solution

Component	Type A[1]	Type B[2]	Type C[3]	Type D[4]
Cations				
Na^+	0–2400	130–160	130–145	130–145
K^+	0–60	2–10	0–4	0–4
Ca^{2+}	0–4	0.5–2.5	0.5–2.0	0–2
Mg^{2+}	0–3	0–1.5	0–1.0	0–1
Anions				
Cl^-	0–2000	90–115	90–120	95–110
HCO_3^-	0–2000	0	0–40	20–55
$P_i^{-1,6}$	0–50.	0	0	
SO_4^{2-}	0–1.2	0		
d-lactate$^-$	0	0	0	
acetate$^-$	0	0	0	
l-lactate$^-$	0–2400	0–55	0–55	0–20
pyruvate$^-$	0–2400	0–55	0–55	0–20
d-betahydroxy-butyrate$^-$	0–2400	0–55	0–55	0–20
acetoacetate$^-$	0–2400	0–55	0–55	0–20
Nonanionics				
Glucose	0–278	0–280	0–240	0–240
pH	5–8.2	6.0–7.5	5–8.2	5.5–8.2

EMBODIMENTS

The following examples are merely illustrative of the present invention and are not intended as a limitation upon the scope thereof.

EXAMPLES 1–4

The following Table III illustrates particular solutions of this invention:

TABLE III

(Values are in mMoles/Liter)

Ex. No.	Component	Class I	Class II	Class III
1	l-lactate[1]	1000		
	Na^+	1000		
2	pyruvate[2]		1000	
	Na^+		1000	
3	l-lactate[3]			900
	pyruvate			100
	Na^+			1000
4	l-lactic acid	5		

Table III footnotes:
[1]For treatment of acidosis see Merck Handbook p 1866 12th edition.
[2]For treatment of acidosis when severe reduction of [NAD$^+$]/[NADH] is present (see USSN 748,232).
[3]For treatment of acidosis when redox balance is desired (see USSN 748,232).
[4]For use as an additive to a bicarbonate containing solution (see USSN 748,232).

EXAMPLES 5–12

Illustrative examples of various physiological abnormalities which are treatable by using various starting solutions of the present invention are shown in Table IV below:

TABLE IV

Exemplary Useages

Condition Where Useful and solution common name	Fluid Composition Cation(s) Anion(s) in mMoles/liter				Route of Administration, and Dose
5. Dehydration (L-lactated Ringers)[1]	Na^+	130	Cl^-	109	parenteral, 500 ml to 3 liters per day depending on severity and cause
	K^+	3	l-lactate$^-$	28	
	Ca^{2+}	1.5			
6. Peritoneal Dialysis (Dianeal[2] w/1.5% Dextrose, Travenol)[3]	Na^+	141	Cl^-	101	Intraperitoneal, 4 to 8, 2 liter bags per day
	Ca^{2+}	1.75	l-lactate$^-$	45	
	Mg^{2+}	0.75			
			(also dextrose 83)		
7. Metabolic Acidosis (Isotonic sodium l-lactate solution)[4]	Na^+	156.1	l-lactate	156.1	parenteral or oral, 10 ml to 1L depending on size of patient
8. Cardiac Reperfusion Fluid[5]	Mg^+	145	Cl^-	115	Intracoronary infusion after cardiac arrest
	Ca^{2+}	0.5	HCO_3^-	25	
	Na^{2+}	0.75	pyruvate$^-$	11.5	
	K^+	4			
		(also glucose 10 and CO_2 1.2)			
9. Dehydration and Potassium Loss[6] in Diarrhea, Ketoacidosis or Stress (Improved Darrow's Solution)[7]	Na+	120.2	Cl^-	104.7	parenteral or oral[8].
	K+	36.2	l-lactate$^-$	51.7	
		(may be diluted with 2 volumes of 278 mMolar glucose for pediatric use)			
10. Hemodialysis with Bicarbonate and l-lactic acid[9]	Na^+	135	Cl^-	106.5	Hemodialysis without unphysiolocal levels of acetate[10]
	K^+	2	HCO_3^-	33	
	Ca^{2+}	1.5	l-lactic		
	Mg^{2+}	0.375	acid	2	
11. Electrolyte Replacement	Na^+	140	Cl^-	103	Alternative to Fox's acetate
	K^+	10	l-lactate	27.5	

TABLE IV-continued

Exemplary Useages					
Condition Where Useful and solution common name	Fluid Composition Cation(s) Anion(s) in mMoles/liter				Route of Administration, and Dose
HBDH-Ringer's	Ca^{2+}	2.5	d-betahy-	27.5	Ringer's
	Mg	1.5	droxybutyrate		for electrolyte replacement[11]

Table IV Footnotes

[1]Hartmann A F. Theory and practice of parenteral fluid administration. JAMA 1934; 103: 1349–1354.

[2]Dianeal is a trade mark of Travenol Laboratories, Deerfield Illinois

[3]Facts and Comparisons. St. Louis: J B Lippincott, Oct 1981–Aug 1983: 35d-53.

[4]Essellier A F, Jeanneret P. Aqueous solutions - parenteral infusion therapy. Documenta Geigy 6th edition. Manchester: Geigy, 1962: 324–334

[5]The period of reperfusion of heart following, for example coronary by pass can be critical and may result in permanent heart damage due to excessive calcium loading. Pyruvate is the preferred substrate for heart under these conditions giving maximal efficiency of cardiac work over either glucose plus l-lactate or glucose alone (See Kobayshi K, Neely J R. The control of maximum rates of glycolysis in rat cardiac muscle. Circ Res 1979; 44: 166–175.

[6]Essellier A F, Jeanneret P. Aqueous solutions - parenteral infusion therapy. Documenta Geigy 6th edition. Manchester: Geigy, 1962: 332–333

[7]Darrow and Pratt. JAMA 1950; 143: 365-ff and 432-ff.

[8]Martin et al. JAMA 1951; 147: 24-ff.

[9]See Table XI, Prior Art Hemodialysis Fluids. WO 86/00227

[10]Blood acetate levels above the physiological level of 0.2 mM are associated with metabolic bone disease. Veech R L. Am J Clin Nutr 44: 544, 1986.

[11]Fox C L. JAMA 1952; 148: 827–833.

It is to be understood that the invention is not limited to the features and embodiments hereinabove specifically set forth, but can be carried out in other ways and manners without departure from its spirit.

I claim:

1. A solution for rehydration, electrolyte replacement, and nutrition comprising water having dissolved therein the following components in the respective quantities indicated:

Component	Quantity (in mM)
Cations	
Na^+	130–160
K^+	2–10
Ca^{2+}	0.5–2.5
Mg^{2+}	0–1.5
Anions	
Cl^-	90–115
pyruvate	0–40
d-beta-hydroxybutyrate$^-$	0–55
acetoacetate$^-$	0–55

provided that in any given said solution,

the pyruvate$^-$, d-beta-hydroxybutyrate$^-$ and acetoacetate$^-$ are the only monoanionic organic metabolic anions present,

the solution does not contain d-beta-hydroxybutyrate$^-$ and acetoacetate$^-$ anions in a ratio of 6:1 to 0.5:1 and

the total amount of pyruvate$^-$, d-beta-hydroxybutyrate$^-$ and acetoacetate$^-$ anions present ranges from about 0.1 to 55 mM with the total amount of said cations being such as to achieve electrical neutrality in any given said solution, and further provided that said solution has a pH ranging from about 6.0 to 7.5.

2. A solution as defined in claim 1 wherein the solution further contains dissolved carbon dioxide.

3. A solution as defined in claim 1 wherein the solution further contains both bicarbonate anion and dissolved carbon dioxide.

4. A solution for dialysis therapy comprising water having dissolved therein the following components in the respective quantities indicated:

Component	Quantity (in mM)
Cations	
Na^+	130–145
K^+	0–4
Ca^{2+}	0.5–2.0
Mg^{2+}	0–1.0
Anions	
Cl^-	90–120
pyruvate$^-$	0–40
d-beta-hydroxybutyrate$^-$	0–55
acetoacetate$^-$	0–55

provided that in any given said solution,

the pyruvate$^-$, d-beta-hydroxybutyrate$^-$ and acetoacetate$^-$ are the only monoanionic organic metabolic anions present,

the solution does not contain d-beta-hydroxybutyrate$^-$ and acetoacetate$^-$ anions in a ratio of 6:1 to 0.5:1

and the total amount of, pyruvate$^-$, d-beta-hydroxybutyrate$^-$ and acetoacetate$^-$ anions present in any given solution ranges from about 0.1 to 55 mM with the total amount of indicated cations present being such as to achieve electrical neutrality, and also provided that said solution has a pH ranging from about 5.0 to 8.2.

5. The solution of claim 4 wherein said solution additionally contains from about 20 to 55 mM of bicarbonate anions and wherein said solution also contains a sufficient portion of at least one of said pyruvate$^-$, d-beta-hydroxybutyrate$^-$ and acetoacetate$^-$ anions which are derived at least in part from the addition to said solution of, respectively, at least one of pyruvic acid, d-beta-hydroxybutyric acid and/or acetoacetic acid in a total amount which is sufficient to produce pH in the range from about 5 to 8.2, and said solution contains sufficient nonionic dissolved nutrients to achieve a milliosmolarity of from about 250 to 550 mOsmole/Liter.

6. The solution of claim 4 wherein said solution additionally contains from about 20 to 55 mM of bicarbonate anions and wherein said solution also contains a sufficient portion of at least one of said pyruvate$^-$, d-beta-hydroxy-butyrate$^-$ and acetoacetate$^-$ anions derived from the addition to said solution of, respectively, at least one of pyruvic acid, d-beta-hydroxybutyric acid and/or acetoacetic acid in a total amount which is sufficient to produce a pH in the range of from about 5.5 to 7.5, and said solution also contains sufficient nonionic dissolved nutrients to achieve a solution milliosmolarity of from about 260 to 550 mOsmoles/Liter.

7. A solution containing at least one anion species selected from the group consisting of pyruvate in an amount so that the concentration of pyruvate$^-$ anions in the fluid is in the range of about 0.01 to 40 millimole per liter, D-β-hydroxybutyrate$^-$, and acetoacetate$^-$, and at least one cation selected from the group consisting of sodium$^+$, potassium$^+$, magnesium^{2+}, calcium^{2+} and ammonium$^+$, the total concentration of all said anions in said solution being in the range from about 0.01 to 2400 millimoles per liter

wherein the solution further comprises one or more of

(a) from about 20 to about 55 millimoles per liter of bicarbonate$^-$ anion,

(b) from about 0.01 to about 2000 millimoles per liter of chloride$^-$ ion,

(c) at least one nonionic dissolved nutrient in an amount sufficient to provide a solution osmolarity in said aqueous solution of from about 250 to about 550 milliosmoles per liter and

(d) dissolved carbon dioxide and provided that the solution does not contain D-p-hydroxybutyrate$^-$ and acetoacetate$^-$ anions in a ratio of 6:1 to 0.5:1.

8. A solution as defined in claim **7** wherein the solution further contains dissolved carbon dioxide.

9. A solution as defined in claim **7**, wherein the solution further contains both bicarbonate anion and dissolved carbon dioxide.

10. A solution of claim **7** wherein the Ph is the range of 5 to 8.2.

11. A solution of claim **7** additionally containing chlorine anion in the range of 0.01 to 2000 millimoles per liter.

12. A solution of claim **7** additionally containing glucose in the range of 0.01 to 540 millimoles per liter.

13. A solution for enteral or parenteral administration to a patient comprising: an electrically neutral aqueous solution of at least one cation and at least one anion, wherein the sole monoanionic organic metabolic anion present in said aqueous solution is pyruvate anion, present in an amount of from about 0.1 to about 40 millimoles per liter of said aqueous solution, said aqueous solution containing substantially no D-lactate or acetate anions, and said aqueous solution having a pH of from about 5 to about 8.2, wherein the solution further comprises one or more of

(a) from about 20 to about 55 millimoles per liter of bicarbonate anion,

(b) from about 0.01 to about 2000 millimoles per liter of chloride ion, and

(c) at least one nonionic dissolved nutrient in an amount sufficient to provide a solution osmolarity in said aqueous solution of from about 250 to about 550 milliosmoles per liter.

14. A solution as defined in claim **13**, further comprising from about 20 to about 55 millimoles per liter of bicarbonate anion.

15. A solution as defined in claim **13**, further comprising from about 0.01 to about 2000 millimoles per liter of chloride ion.

16. A solution as defined in claim **13**, further comprising at least one nonionic dissolved nutrient in an amount sufficient to provide a solution osmolarity in said aqueous solution of from about 250 to about 550 milliosmoles per liter.

17. A solution as defined in claim **13**, wherein said at least one cation is selected from the group consisting of sodium ions, potassium ions, calcium ions, magnesium ions, and mixtures of sodium ions with any of potassium ions, calcium ions and magnesium ions.

18. A solution for enteral or parenteral administration to a patient comprising: an electrically neutral aqueous solution of at least one cation and at least one anion, wherein the sole monoanionic organic metabolic anion present in said aqueous solution is D-β-hydroxybutyrate anion, present in an amount of from about 0.1 to about 55 millimoles per liter of said aqueous solution, said aqueous solution containing substantially no D-lactate or acetate anions, and said aqueous solution having a pH of from about 5 to about 8.2, wherein the solution further comprises one or more of

(a) from about 20 to about 55 millimoles per liter of bicarbonate anion,

(b) from about 0.01 to about 2000 millimoles per liter of chloride ion, and

(c) at least one nonionic dissolved nutrient in an amount sufficient to provide a solution osmolarity in said aqueous solution of from about 250 to about 550 milliosmoles per liter.

19. A solution as defined in claim **18**, further comprising from about 20 to about 55 millimoles per liter of bicarbonate anion.

20. A solution as defined in claim **18**, further comprising from about 0.01 to about 2000 millimoles per liter of chloride ion.

21. A solution as defined in claim **18**, further comprising at least one nonionic dissolved nutrient in an amount sufficient to provide a solution osmolarity in said aqueous solution of from about 250 to about 550 milliosmoles per liter.

22. A solution as defined in claim **18**, wherein said at least one cation is selected from the group consisting of sodium ions, potassium ions, calcium ions, magnesium ions, and mixtures of sodium ions with any of potassium ions, calcium ions and magnesium ions.

23. A solution for enteral or parenteral administration to a patient comprising: an electrically neutral aqueous solution of at least one cation and at least one anion, wherein the sole monoanionic organic metabolic anion present in said aqueous solution is acetoacetate anion, present in an amount of from about 0.1 to about 55 millimoles per liter of said aqueous solution, said aqueous solution containing substantially no D-lactate or acetate anions, and said aqueous solution having a pH of from about 5 to about 8.2, wherein the solution further comprises one or more of

(a) from about 20 to about 55 millimoles per liter of bicarbonate anion,

(b) from about 0.01 to about 2000 millimoles per liter of chloride ion, and

(c) at least one nonionic dissolved nutrient in an amount sufficient to provide a solution osmolarity in said aqueous solution of from about 250 to about 550 milliosmoles per liter.

24. A solution as defined in claim **23**, further comprising from about 20 to about 55 millimoles per liter of bicarbonate anion.

25. A solution as defined in claim **23**, further comprising from about 0.01 to about 2000 millimoles per liter of chloride ion.

26. A solution as defined in claim **23**, further comprising at least one nonionic dissolved nutrient in an amount sufficient to provide a solution osmolarity in said aqueous solution of from about 250 to about 550 milliosmoles per liter.

27. A solution as defined in claim **23**, wherein said at least one cation is selected from the group consisting of sodium ions, potassium ions, calcium ions, magnesium ions, and mixtures of sodium ions with any of potassium ions, calcium ions and magnesium ions.

28. A solution for rehydration, electrolyte replacement, and nutrition comprising water having dissolved therein the following components in the respective quantities indicated:

Component	Quantity (in mM)
Cations	
Na^+	130–160
K^+	2–10
Ca^{2+}	0.5–2.5
Mg^{2+}	0–1.5
Anions	
Cl^-	90–115,

and as a sole monoanionic organic metabolic anion present in said solution, a monoanionic organic metabolic anion selected from the group consisting of pyruvate, D-β-hydroxybutyrate and acetoacetate, said organic metabolic anion being present in an amount of from about 0.1 to about 55 millimoles per liter of solution, except for pyruvate which may be present in an amount of from about 0.1 to about 40 millimoles per liter of said solution, said solution containing substantially no D-lactate or acetate anions, the total amount of said cations present in said solution being sufficient to provide electrical neutrality and said solution having a pH of from about 6.0 to about 7.5.

29. A solution for dialysis therapy comprising water having dissolved therein the following components in the respective amounts indicated:

Component	Quantity (in mM)
Cations	
Na^+	130–145
K^+	0–4
Ca^{2+}	0.5–2.0
Mg^{2+}	0–1.0
Anions	
Cl^-	90–120,

and as a sole monoanionic organic metabolic anion present in said solution, a monoanionic organic metabolic anion selected from the group consisting of pyruvate, D-β-hydroxybutyrate and acetoacetate, said organic metabolic anion being present in an amount of from about 0.1 to about 55 millimoles per liter of solution, except for pyruvate which may be present in an amount of from about 0.1 to about 40 millimoles per liter of said solution, said solution containing substantially no D-lactate or acetate anions, the total amount of said cations present in said solution being sufficient to provide electrical neutrality and said solution having a pH of from about 5 to about 8.2.

30. A solution for rehydration, electrolyte replacement and nutrition comprising water having dissolved therein the following components in the respective quantities indicated:

Component	Quantity (in mM)
Cations	
Na^+	130–160
K^+	2–10
Ca^{2+}	0.5–2.5
Mg^{2+}	0–1.5
Anions	
Cl^-	90–115

and a further sole monoanionic metabolic anion consisting of d-betahydroxybutyrate$^-$ provided that in any given solution the total amount of said d-betahydroxybutyrate$^-$ present in any given solution ranges from about 0.1 to 55 mM with the total amount of said cations being such as to achieve electrical neutrality in any given said solution, and further provided that said solution has a pH ranging from about 6.0 to 7.5;

wherein the solution further comprises one or more of

(a) from about 20 to about 55 millimoles per liter of bicarbonate$^-$ anion,

(b) from about 0.01 to about 2000 millimoles per liter of chloride$^-$ ion,

(c) at least one nonionic dissolved nutrient in an amount sufficient to provide a solution osmolarity in said aqueous solution of from about 250 to about 550 milliosmoles per liter and;

(d) dissolved carbon dioxide.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Leo Martis et al.	DOCKET NO.:	P94,1481-B
SERIAL NO.:	08/421,020	GROUP ART UNIT:	1204
FILED:	April 12, 1995	EXAMINER:	R.A. Williams

TITLE: "BIOCHEMICALLY BALANCED PERITONEAL DIALYSIS SOLUTIONS"

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF LEO MARTIS, Ph.D.

S I R:

I, Leo Martis, Ph.D., hereby declare as follows:

1. I am a co-inventor of U.S. Patent Application Serial No. 08/421,020. I earned a Ph.D. in Pharmacology in 1973. I have been a research chemist at Baxter International Inc. since 1974 and have been a research scientist working in the field of peritoneal dialysis solutions since 1978.

2. I have reviewed the Office Action mailed on August 20, 1996 which rejects the claims of Application Serial No. 08/421,020 in light of the Schambye, Zander and Veech references. I have reviewed the Schambye and Zander references thoroughly and make the following statements as a person skilled in the art of peritoneal dialysis.

3. The Schambye article is allegedly directed toward the optimization of peritoneal dialysis solutions with respect to their effect on normal human polymorphonuclear granulocytes *in vitro*. The Schambye article and the solutions disclosed in the article are not designed or intended to correct metabolic acidosis associated with end stage renal disease. Because Schambye allegedly discloses a solution with a pH of 7.0-7.2 and with a carbonate and lactate concentration of 20 mM and 12.5 mM respectively with no carbon dioxide partial pressure, Schambye does not suggest a composition with the buffer qualities or the ability to maintain the acid-base balance in a patient that is achieved by the example shown at Example 1 at pages 9-10 of the present application. Further,

because Schambye does not suggest using a partial pressure of carbon dioxide.

4. I have also thoroughly reviewed the Zander reference. In the discussion of the "preliminary research" at column 2, line 35-43, Zander discloses a dialysis solution having a pH value of 7.4 +/- 0.5 with a bicarbonate concentration of 24 mmole/l and a carbon dioxide partial pressure of 40 mmHg. However, because this specific combination lacks a weak acid, one skilled in the art would readily recognize the solution disclosed at column 2 of the Zander reference would not be effective in maintaining the acid-base balance in peritoneal dialysis patients. While the Zander preliminary solution may prevent the loss of bicarbonate from the body, it would be deficient in terms of neutralizing the hydrogen ions generated endogenously by the dialysis patient as a result of protein metabolism.

5. Zander allegedly discloses another dialysis solution at column 6, lines 47-53 which is a combination of an acid-containing solution and a base-containing solution. This combination solution has a pH of 7.4, a bicarbonate concentration of 24.0 mmole/l and an acetate concentration of 27.2 mmole/l. However, this proposed solution is unable to maintain the acid-base balance in dialysis patients because the concentration of the weak acid (acetic acid) is too high.

6. Further, it has long been known that acetate damages the peritoneal membrane causing loss of ultrafiltration, see Faller and Marichal, "Loss of Ultrafiltration in Continue Ambulatory Peritoneal Dialysis: A Role for Acetate", *Peritoneal Dialysis Bulletin*, Jan.-Mar. 1984. In any event, if another weak acid was substituted for acetic acid, the concentration would still be too high which would result in a solution unable to maintain the acid-base balance in a peritoneal dialysis patient. As a result, the Zander patent is not credible and the solutions disclosed in the

Zander patent suggest that no thought has been given to the buffer content required to maintain the acid-base balance.

7. In contrast, the unique combination of the buffers and their concentrations of the present invention result in a peritoneal dialysis solution, as exemplified by Example 1 of the present application, that maintains the acid-base balance in a peritoneal dialysis patient suffering from end stage renal disease. The efficacy and safety of the solutions of the present invention have been proven in a clinical study.

8. Specifically, a clinical study was performed with the solution described in Example 1 of the present application. Twelve continuous ambulatory patients used the solution daily for eight weeks. Mean serum bicarbonate levels for the twelve patients were as follows:

	Concentration (mEq/L)
Day 0	25.3 +/- 3.4
Week 4	26.5 +/- 3.8
Week 8	26.6 +/- 3.4

Thus, the mean serum bicarbonate levels for the twelve patients during the eight week treatment period was within the normal range of 24-32 mEq/L.

9. The biocompatibility of the solution described in Example 1 of the present application was compared with that of currently used solutions in clinical practice, specifically the solution sold under the DIANEAL trademark. The following table shows the effect of a 30 minute exposure on human peripheral blood polymorphonuclear leukocyte viability (ATP content) and function (phagocytosis):

% of Control (M199 media plus 0.1%FCS)

	ATP content	Phagocytosis
DIANEAL	48.0 +/- 22.2	17.3 +/- 10.2
Example 1	111.4 +/- 40.4	48.6 +/- 19.3

A comparison of the solution of Example 1 and the DIANEAL solution is as follows:

	Example 1	DIANEAL
Dextrose (gm/dl)	1.5	1.5
Sodium (mEq/L)	132	132
Chloride (mEq/L)	96	96
Calcium (mEq/L)	3.5	3.5
Magnesium (mEq/L)	0.5	0.5
Lactate (mEq/L)	15.0	40.0
Bicarbonate (mEq/L)	25.0	____

10. The above results suggest that a unique combination of bicarbonate, lactate, and carbon dioxide partial pressure as described in the present invention and exemplified by Example 1 of the present application is essential to both maintain the acid-base balance of dialysis patients and further to improve biocompatibility.

11. As one skilled in the art, I can state that neither the solutions disclosed in Schambye nor the solutions disclosed in Zander, nor any combination thereof, can provide a dialysis solution that can maintain the acid-base balance of a dialysis patient. Further, Zander does not address the need for improved biocompatibility of peritoneal dialysis solutions and therefore no combination of Schambye and Zander provides a peritoneal dialysis solution that both maintains an acid-base balance in a peritoneal dialysis patient and also provides improved biocompatibility.

I hereby declare that all statements made herein are of my own knowledge and are true and that all statements made on information and belief are believed to be true. I also make this declaration with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and further that any such willful false statements and the like may jeopardize the validity of this application or any patent issuing thereon.

Date: 12-13-96

Leo Martis

Leo Martis, Ph.D.